THERAPEUTIC ADVANCES in
Medical Oncology

Review

The continually evolving landscape of novel therapies in oncogene-driven advanced non-small-cell lung cancer

Ther Adv Med Oncol

2025, Vol. 17: 1–40

DOI: 10.1177/17588359241308784

Barbara Melosky, **Rosalyn A. Juergens**, **Shantanu Banerji**, **Adrian Sacher**, **Paul Wheatley-Price**, **Stephanie Snow**, **Ming-Sound Tsao**, **Natasha B. Leighl**, **Ilidio Martins**, **Parneet Cheema**, **Geoffrey Liu** and **Quincy S. C. Chu**

***Abstract*:** Non-small-cell lung cancer (NSCLC) is a highly heterogeneous disease that is frequently associated with a host of known oncogenic alterations. Advances in molecular diagnostics and drug development have facilitated the targeting of novel alterations such that the majority of NSCLC patients have driver mutations that are now clinically actionable. The goal of this review is to gain insights into clinical research and development principles by summary, analysis, and discussion of data on agents targeting known alterations in oncogene-driven, advanced NSCLC beyond those in the *epidermal growth factor receptor (EGFR)* and the *anaplastic lymphoma kinase (ALK)*. A search of published and presented literature was conducted to identify prospective trials and integrated analyses reporting outcomes for agents targeting driver gene alterations (except those in *EGFR* and *ALK*) in molecularly selected, advanced NSCLC. Clinical efficacy data were extracted from eligible reports and summarized in text and tables. Findings show that research into alteration-directed therapies in oncogene-driven, advanced NSCLC is an extremely active research field. Ongoing research focuses on the expansion of new agents targeting both previously identified targets (particularly hepatocyte growth factor receptor (MET), human epidermal growth factor receptor 2 (HER2), and Kirsten rat sarcoma viral oncogene homolog (KRAS)) as well as novel, potentially actionable targets (such as neuregulin-1 (NRG1) and phosphatidylinositol 3-kinase (PI3K)). The refinement of biomarker selection criteria and the development of more selective and potent agents are allowing for increasingly specific and effective therapies and the expansion of clinically actionable alterations. Clinical advances in this field have resulted in a large number of regulatory approvals over the last 3 years. Future developments should focus on the continued application of alteration therapy matching principles and the exploration of novel ways to target oncogene-driven NSCLC.

Keywords: antibody–drug conjugates, monoclonal antibodies, non-small-cell lung cancer, oncogenic alterations, protein kinase inhibitors, targeted therapy

Received: 9 October 2024; revised manuscript accepted: 5 December 2024.

Correspondence to:
Barbara Melosky
Medical Oncology, BC Cancer Agency—Vancouver, University of British Columbia, 600 West 10th Avenue, Vancouver, BC V5Z 4E6, Canada
bmelosky@bccancer.bc.ca

Rosalyn A. Juergens
Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada

Shantanu Banerji
Paul Albrechtsen Research Institute, CancerCare Manitoba, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

Adrian Sacher
Natasha B. Leighl
Geoffrey Liu
Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Paul Wheatley-Price
Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

Stephanie Snow
QEII Health Sciences Centre, Dalhousie University, Halifax, NS, Canada

Ming-Sound Tsao
University Health Network and Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Ilidio Martins
Kaleidoscope Strategic Inc., Toronto, ON, Canada

Parneet Cheema
William Osler Health System, University of Toronto, Brampton, ON, Canada

Quincy S. C. Chu
Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada

Introduction

Lung cancer is one of the most common malignancies and the leading cause of cancer-related death.[1–3] Non-small-cell lung cancer (NSCLC) accounts for 85% of all lung malignancies and approximately 50% of NSCLC patients are diagnosed at the metastatic stage.[4–6]

NSCLC is a heterogeneous disease that is frequently associated with multiple known oncogenic driver genes.[7–10] The earliest characterized of these are mutations involving the *epidermal growth factor receptor* (*EGFR*) and fusions involving *anaplastic lymphoma kinase* (*ALK*). Treatment with EGFR and ALK inhibitors is well established, with initial

approvals in biomarker-unselected and -selected populations in 2003 and 2011, respectively.[7,11–14]

Advances in cancer biology, molecular diagnostics, and drug development have improved our ability to identify and therapeutically target oncogenic alterations.[9,10,15,16] It is now estimated that the majority of NSCLC patients have alterations that are clinically actionable with a therapeutic agent that acts on the altered target (alteration-drug-matched).[9,17–26] Here we will update our initial review of novel (non-EGFR/ALK) targeted therapies[8] by identifying, summarizing, analyzing, and discussing recent data on agents targeting lesser-known alterations (Table 1) in oncogene-driven, advanced NSCLC to gain insights into clinical research and development principles.

Table 1. Select actionable molecular alterations in oncogene-driven NSCLC.

Oncogene and molecular alteration	Biological function in regular and altered states	Common alterations	Incidence, %	Detection method
ROS1 rearrangement[7,9,27–29]	• ROS1 is a tyrosine kinase receptor with significant structural homology to ALK • Rearrangements/translocations give rise to fusions of functional ROS1 tyrosine kinase domain with other genes • Resulting constitutive activation drives transformation and activates SHP-1/SHP-2, JAK/STAT, PI3K/AKT/mTOR, and MAPK/ERK signaling leading to enhanced tumor cell survival and proliferation	Up to 24 fusion partners identified	1–3	FISH, RT-PCR, RNA NGS
BRAF-V600 mutation[7,9,30]	• BRAF is an intracellular serine/threonine kinase activated by RAS and subsequently activates MEK and ERK (MAPK pathway) • Mutation leads to constitutive activation, cell growth, and proliferation • Dual inhibition of BRAF and MEK may prevent reactivation of MAPK signaling	V600E	1–2	DNA NGS
NTRK rearrangement[7,9,31–34]	• Neurotrophin kinase genes (*NTRK1*, *NTRK2*, and *NTRK3*) code for tropomyosin receptor tyrosine kinases (TRKA, TRKB, and TRKC) • Ligand binding activates PI3K/AKT/mTOR, RAS/RAF/MAPK, and PLC-γ pathways, leading to the proliferation, growth, and survival of neurons in the peripheral and central nervous system • Gene rearrangements result in the formation of fusion proteins that drive tumor growth and survival through constitutively active forms containing the TRK kinase domain	*NTRK1* *NTRK2* *NTRK3*	0.1–1(3)	FISH, RT-PCR, DNA/RNA NGS
MET alteration[7,9,35]	• MET regulates cell growth, differentiation, motility, and epithelial–mesenchymal transition in tumor cells through activation of RAS/RAF/MAPK, PI3K/AKT/mTOR, WNT/β-catenin, and STAT pathways • MET gene amplification may result in constitutive activation of MET receptor • MET amplification is also a driver of acquired resistance to EGFR TKIs • MET exon 14 skipping mutations lead to decreased MET degradation, leading to high expression and increased activation	*MET* amplification (MET/CEP7 ratio >2 or GCN >5) *MET* exon 14 skipping mutation	0.34 2–3	FISH DNA NGS
RET rearrangement[7,9,36,37]	• RET is a tyrosine kinase receptor with giant cell-derived neurotrophic factor as its ligand • Activation leads to RAS/RAF/MAPK, PI3K/AKT/mTOR, and PLC-signaling → cell proliferation, migration, and differentiation • Chromosomal rearrangements involve fusion partners such as KIF5B, CCDC6, NCOA4, and TRIM33 • Chimeric proteins constitutively dimerize, activating the kinase domain and leading to uncontrolled activation of MAPK and PI3K pathways	13 RET/PTC fusion proteins identified (RET/PTC1-PTC9)	1–2	FISH, DNA/RNA NGS RT-PCR

(Continued)

Table 1. (Continued)

Oncogene and molecular alteration	Biological function in regular and altered states	Common alterations	Incidence, %	Detection method
HER2 alteration[7,9,38–40]	• Altered ErbB, or HER, signaling has been implicated in many forms of cancer. HER2 is an emerging target for NSCLC • HER2 is an ErbB receptor tyrosine kinase. The binding of ligands to ErbB members induces homo- and heterodimerization and activation of downstream PI3K/AKT signaling → cellular proliferation, migration, and differentiation • Changes leading to altered HER signaling include HER2 amplification and mutations	*HER2* amplification	2–22	FISH
		HER2 overexpression	8–23	IHC
		HER2 exon 20 duplication or YVMA 776–779 insertion (80%–90%)	1–7	DNA NGS
		HER2 rare point mutations: G660D, R678Q, E693K, and Q709L		
KRAS mutation[7,9,41–44]	• KRAS activated by GDP → GTP binding • KRAS-GTP → MAPK/ERK and KRAS mutations prevent hydrolysis (KRAS-GTP → inactive KRAS-GDP) persistent activation of MAPK/ERK and PI3K • KRAS is a downstream effector of EGFR which can promote tumor cell proliferation	Point mutation at codons 12 (most common, >80%), 13, 14, and 60/61	Up to 30 KRASG12C: 3–15	DNA NGS

Source: Adapted from Melosky et al.[8]
AKT, protein kinase B; ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CCDC6, coiled-coil domain-containing protein 6; CEP, centromere of chromosome 7; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; ErbB, avian erythroblastic leukemia viral oncogene homolog; ERK, extracellular-signal-regulated kinase; FISH, fluorescence in situ hybridization; GCN, gene copy number; GDP, guanosine diphosphate; GTP, guanosine triphosphate; HER2/3, human epidermal growth factor receptor 2/3; JAK, Janus kinase; KIF5B, kinesin family member 5B; KRAS, Kirsten rat sarcoma viral oncogene homolog; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; MET, hepatocyte growth factor receptor; mTOR, mammalian target of rapamycin; NCOA4, nuclear receptor coactivator 4; NGS, next-generation sequencing; NSCLC, non-small-cell lung cancer; NTRK1/2/3, neurotrophic tyrosine receptor kinase 1/2/3; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; PTC, papillary thyroid carcinomas; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma GTPase; RET, rearranged during transfection; RNA, ribonucleic acid; ROS1, c-ros oncogene 1; RT-PCR, reverse transcription polymerase chain reaction; SHP-1/2, Src homology 2 domain-containing protein tyrosine phosphatase 1/2; STAT, signal transducer and activator of transcription; TKI, tyrosine kinase inhibitor; TRIM33, tripartite motif containing 33; TRKA/B/C, tropomyosin receptor kinase A/B/C; WNT, wingless-related integration site.

Methods

We have elected to support this narrative review with systematic search methods to ensure unbiased and comprehensive identification, assessment, and summary of relevant clinical studies in this field. A search of published and presented literature was conducted to identify prospective phase I–III trials and integrated analysis reporting efficacy outcomes for agents targeting novel driver gene alterations (i.e., excluding *EGFR* and *ALK*) in molecularly selected, advanced NSCLC populations. PubMed (all time to October 25, 2023), the proceedings from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the World Conference on Lung Cancer 2022 and 2023 annual meetings were searched using the key search terms "NSCLC" AND "advanced"/"metastatic" AND "novel targets" AND "phase I–III" OR respective aliases (Figure 1). A supplemental bibliographic search of review articles and pooled/meta-analyses was also conducted. In addition, directed searches were performed after the database search cutoff date to ensure that the most up-to-date reports of eligible studies were considered. English language records were vetted at the abstract level and checked at the full text as needed by an initial reviewer (A.P.) and confirmed by a second independent reviewer (I.M.). All eligible studies were cited in the findings; however, only trials reporting outcomes since our initial review[8] (i.e., in the last 3 years, approximately) for at least 20 patients with alteration-drug-matched NSCLC were included in the tables. Additional search and vetting details are summarized in Supplemental Methods.

Findings

The literature search identified a total of 2938 records, resulting in a total of 180 primary reports

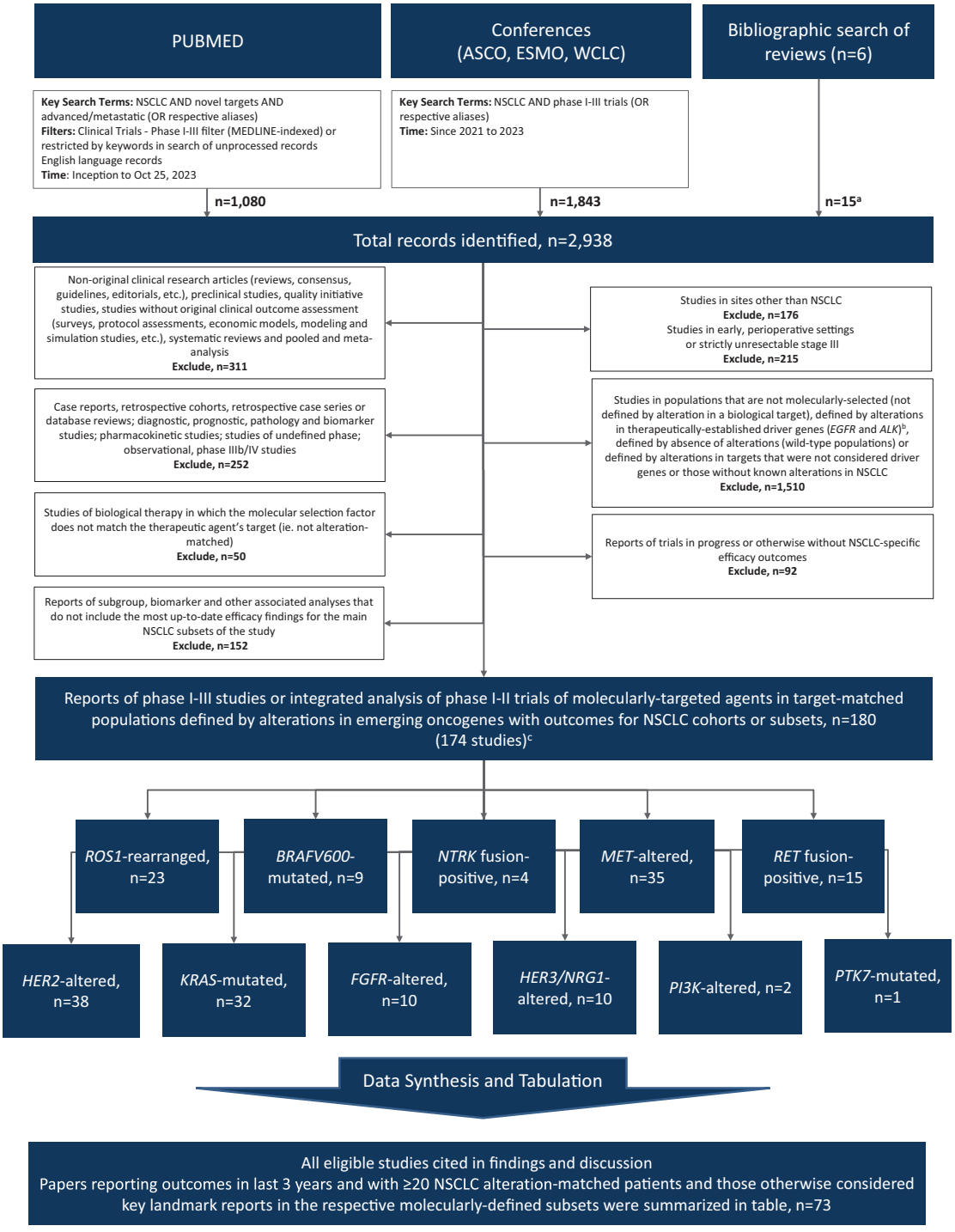

Figure 1. PRISMA diagram.
[a]Primary or associated reports of eligible studies that were not identified through database search.
[b]All types of ALK and EGFR alterations were included.
[c]A single trial may have multiple reports for different biomarker-selected patient cohorts or subsets; likewise, a single report may provide data from single or multiple studies on different biomarker-selected patient cohorts or subsets.
ALK, anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology; BRAF, v-raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, hepatocyte growth factor receptor; n, number; NRG1, neuregulin-1; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; Pl3K, phosphoinositide 3-kinase; PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PTK7, tyrosine-protein kinase-like 7; RET, rearranged during transfection; ROS1, c-ros oncogene 1; WCLC, World Conference on Lung Cancer.

Table 2. Efficacy outcomes of clinical trials assessing novel targeted therapy in molecularly selected, target-matched advanced NSCLC.

Trial name, NCT# Phase	Molecular alteration	Line of therapy Pretreatment details	Regimen(s)	Patients, *n*	Overall response rate,[a] % (95% CI)	Median duration of response,[a] months (95% CI)	Median progression-free survival,[a] months HR (95% CI)	Median overall survival, months HR (95% CI)
ROS1-rearranged								
ROS1-TKI-naïve								
EUCROSS, NCT02183870 Phase II[45–47]	*ROS1* rearrangement	First/Second line+ ROS1 TKI-naïve	Crizotinib 250 mg BID	30	73.3 (54.1–87.7)	19.0 (8.3–NYR)	19.4[b] (10.1–32.2)	54.8 (20.3–NYR)
METROS, NCT02499614 Phase II Study + Expansion Cohorts[48,49]	*ROS1* rearrangement	Second line+ ROS1 TKI-naïve	Crizotinib 250 mg BID	64	65.4[b,c] (44–82)	21.4[b,c] (12.7–30.1)	13.8[b] (7.4–20.2)	40.5 (27.9–53.1)
OO 12-01, NCT01945021 Phase II[50,51]	*ROS1* rearrangement, *ALK* rearrangement negative	First line+	Crizotinib 250 mg BID	127	71.7 (63.0–79.3)	19.7 (14.1–NYR)	15.9 (12.9–24.0)	44.2 (32.0–NYR)
STARTRK-2, STARTRK-1, and ALKA-372-001 Integrated Analysis[52]	*ROS1* rearrangement	First/second line+ TKI-naïve	Entrectinib 600 mg daily	168	67.9 (60.2–74.8)	20.5 (14.8–34.8)	15.7 (12.0–21.1)	47.8 (44.1–NE)
TQ-B3101-1-0001/TQ-B3101-II-01, NCT03019276/ NCT03972189 Phase I/II[53]	*ROS1* rearrangement	First line+	Unecritinib 300 mg BID	111	80.2 (71.5–87.1)	20.3 (11.0–26.1)	16.5 (10.2–27.0)	NR
Barossa, JapicCTI-194851 Phase II Cohort 1[54]	*ROS1* rearrangement	First line TKI-naïve	Brigatinib 180 mg daily[d]	28	67.9 (90% CI, 50.6–82.1)	NR	12.0 (5.8–NE)	NYR
BTP-42723, NCT03608007 Phase II[55]	*ROS1* rearrangement	First/second line TKI-naïve	Ensartinib 225 mg daily	37	27.0[b] (13.8–44.1)	4.8[b] (1.8–10.8)	4.6[b] (4.0–6.4)	NYR (14.9–NE)
TRIDENT-1, NCT03093116 Phase I/II[56]	*ROS1* rearrangement	First line+ TKI naïve	Repotrectinib 40 mg daily to 160 mg BID, including the R2PD of 160 mg QD × 14 days followed by 160 mg BID	71	79 (68–88)	34.1 (25.6–NE)	35.7 (27.4–NE)	NE (44.4–NE)
TRUST, NCT04395677 Phase II[57]	*ROS1* rearrangement	First line+ TKI-naïve	Taletrectinib 600 mg daily	67	92.5 (83.4–97.5)	NYR (range: 1.3–27.6)	NYR (range: 0.0–29.0)	NR
TRUST-II, NCT04919811 Phase II[58]	*ROS1* rearrangement	First line+ ROS1-TKI-naïve	Taletrectinib 600 mg daily	25	92.0 (74.0–99.0)	NR	NR	NR
TKI-pretreated								
TRIDENT-1, NCT03093116 Phase I/II[56]	*ROS1* rearrangement	Second line 1 Prior TKI, no prior CT	Repotrectinib 40 mg daily to 160 mg BID, including the RP2D of 160 mg QD × 14 days followed by 160 mg BID	56	38 (25–52)	14.8 (7.6–NE)	9.0 (6.8–19.6)	25.1 (17.8–NE)
TRUST, NCT04395677 Phase II[57]	*ROS1* rearrangement	Second line+ Crizotinib-pretreated	Taletrectinib 600 mg daily	38	52.6 (35.8–69.0)	NYR (range: 1.4–22.2)	9.8 (range: 0.0–23.5)	NR

(Continued)

Table 2. (Continued)

Trial name, NCT# Phase	Molecular alteration	Line of therapy Pretreatment details	Regimen(s)	Patients, *n*	Overall response rate,[a] % (95% CI)	Median duration of response,[a] months (95% CI)	Median progression-free survival,[a] months HR (95% CI)	Median overall survival, months HR (95% CI)
TRUST-II, NCT04919811 Phase II[58]	*ROS1* rearrangement	Second line ⩾1 prior ROS1-TKI	Taletrectinib 600 mg daily	21	57.1 (34.0–78.2)	NR	NR	NR
ARROS-1, NCT05118789 Phase I[59]	*ROS1* rearrangement	Second line ⩾1 prior ROS1-TKI	NVL-520 25–125 mg daily	21	48	NR	NR Median time on treatment: 3.6	NR
BRAF mutant								
BRF113928, NCT01336634 Phase II[60–62]	*BRAF* V600E-mutation	First line	Dabrafenib 150 mg BID plus trametinib 2 mg QD	36	63.9[b] (46.2–79.2)	10.2[b] (8.3–15.2)	10.8[b] (7.0–14.5)	17.3 (12.3–40.2)
		Second line+	Dabrafenib 150 mg BID plus trametinib 2 mg QD	57	68.4[b] (54.8–80.1)	9.8[b] (6.9–18.3)	10.2[b] (6.9–16.7)	18.2 (14.3–28.6)
CDRB436ECN01, NCT04452877 Phase II[63]	*BRAF* V600E-mutation	First line+	Dabrafenib 150 mg BID plus trametinib 2 mg QD	20	75 (50.9–91.3)	NYR	NYR	NYR
PHAROS, NCT03915951 Phase II[64]	*BRAF* V600E-mutation	First line	Encorafenib 450 mg QD plus Binimetinib 45 mg BID	59	75 (62–85)	NYR (23.1–NE)	NYR (15.7–NE)	NYR
		Second line+		39	46 (30–63)	16.7 (7.4–NE)	9.3 (6.2–NE)	NYR
HL-085-102, NCT03781219 Phase I[65]	*BRAF* V600-mutation	Second line+	Tunlametinib 0.5 to 15 mg BID plus vemurafenib 960 mg BID q3w in dose escalation phase Tunlametinib 9/12 mg BID plus vemurafenib 720/960 mg BID in dose expansion phase	33	60.6[e] (42.1–77.1)	11.3[e] (3.9–NE)	11.7[e] (5.6–NE)	NR
NTRK-rearranged								
LOXO-TRK-14001, NAVIGATE and SCOUT Integrated analysis[66]	*NTRK* rearrangement	Lung subgroup First-line+	Larotrectinib 100 mg BID	20	73[b] (45–92)	33.9[b] (5.6–33.9)	35.4[b] (5.3–35.4)	40.7 (17.2–NE)
STARTRK-2, STARTRK-1 and ALKA-372-001 Integrated analysis[67]	*NTRK* rearrangement	Lung subgroup First line+	Entrectinib 600 mg QD	51	62.7 (48.1–75.9)	27.3 (19.9–30.9)	28.0 (15.7–30.4)	41.5 (30.9–NE)
TRIDENT-1, NCT03093116 Phase II[68]	*NTRK* rearrangement	TKI naïve (52%)	Repotrectinib 160 mg QD × 2 weeks → 160 mg BID	21	62 (38–82)	12 mos DoR: 92% (76–100)	12 mos PFS: 64% (43–86)	NR
		TKI pretreated (29%)	Repotrectinib 160 mg QD × 2 weeks → 160 mg BID	14	42 (18–71)	12 mos DoR: 44% (1–88)	12 mos PFS: 23% (0–49)	NR

(Continued)

Table 2. (Continued)

Trial name, NCT# Phase	Molecular alteration	Line of therapy Pretreatment details	Regimen(s)	Patients, *n*	Overall response rate,[a] % (95% CI)	Median duration of response,[a] months (95% CI)	Median progression-free survival,[a] months HR (95% CI)	Median overall survival, months HR (95% CI)
MET-altered								
MET-amplified, overexpressed, and/or mutated								
PROFILE 1001, NCT00585195 Phase I[69]	*MET* amplification, MET/CEP7 ratio ⩾1.8	First-line+	Crizotinib 250 mg BID	38	28.9[b] (15.4–45.9) *MET/CEP7 ratio ⩾4.0: 38.1 (18.1–61.6)*	5.2[b] (range: 3.3–25.8) *MET/CEP7 ratio ⩾4.0: 5.2 (range: 3.3–25.8)*	5.1[b] (1.9–7.0) *MET/CEP7 ratio ⩾4.0: 6.7 (3.4–9.2)*	11.0 (7.1–15.9) *MET/CEP7 ratio ⩾4.0: 11.4 (7.2–19.3)*
GEOMETRY mono-1, NCT02414139 Phase II[70]	*MET* amplification, GCN ⩾10	Cohort 1a Second line+	Capmatinib 400 mg BID	69	29 (19–41)	8.3 (4.2–15.4)	4.1 (2.9–4.8)	NR
	MET amplification, GCN 6 to 9	Cohort 1b Second line+	Capmatinib 400 mg BID	42	12 (4–26)	24.9 (2.7–24.9)	2.7 (1.4–3.1)	NR
	MET amplification, GCN 4 or 5	Cohort 2 Second line+	Capmatinib 400 mg BID	54	9 (3–20)	9.7 (4.2–NE)	2.7 (1.4–4.1)	NR
	MET amplification, GCN <4	Cohort 3 Second line+	Capmatinib 400 mg BID	30	7 (1–22)	4.2 (4.2–4.2)	3.6 (2.2–4.2)	NR
	MET amplification, GCN ⩾10	Cohort 5a First line	Capmatinib 400 mg BID	15	40 (16–68)	7.5 (2.6–14.3)	4.2 (1.4–6.9)	NR
VISION, NCT02864992 Cohort B Phase II[71]	*MET* amplification, GCN ⩾2.5	First line+	Tepotinib 500 mg QD	24	42	NE (2.8–NE)	NR	NR
16-019, NCT02750215 Phase II[72]	*MET* skipping alterations (75%) or amplification (25%)	Crizotinib pretreated	Capmatinib 400 mg BID	20	10[e]	NR	5.5[e] (1.3–11.0)	11.3 (5.5–NYR)
265-101, NCT00697632 Phase I[73]	*MET/AXL* mutation or amplification	First line+	Glesatinib spray-dried dispersion (750 mg BID) and free-base suspension (1050 mg BID) formulations	27	25.9[e]	NR	4.1[e]	9.7
BD-CM-I02, NCT02929290 Phase Ib[74]	c-MET overexpression *and/or MET*ex14 skipping mutation	First line+	BPI-9016M 300–600 mg QD or 400 mg BID	38	2.6[e] (0.1–13.8)	NR	1.9[e] (1.9–3.7)	10.3 (7.3–NE)
R5093-ONC-1863, NCT04077099 Phase I[75]	*MET*ex14 skipping, *MET* amplification (GCN ⩾ 6 or *MET/CPC7* ⩾ 4, or *MET* gene fold change ⩾ 2), or overexpression (IHC3+ or H score ⩾200)	First line+	REGN5093 2000 mg q3w	36	16.7[e]	NR	NR	NR

(Continued)

Table 2. (Continued)

Trial name, NCT# Phase	Molecular alteration	Line of therapy Pretreatment details	Regimen(s)	Patients, *n*	Overall response rate,[a] % (95% CI)	Median duration of response,[a] months (95% CI)	Median progression-free survival,[a] months HR (95% CI)	Median overall survival, months HR (95% CI)
LUMINOSITY, NCT03539536 Phase II[76]	c-MET overexpression	Second line+	Telisotuzumab Vedotin 1.9 mg/kg q2w	122	22.1 NSQ EGFR WT: 36.5 (23.6–51.0) NSQ EGFR mutant: 11.6 (3.9–25.1) SQ: 11.1 (2.4–29.2)	NR NSQ EGFR WT: 6.9 (4.1–NE) NSQ EGFR mutant: NE (3.0–NE) SQ: 4.4 (3.0–NE)	NR	NR
LUNG-MAP, NCT02154490 Phase II (platform) Sub-study S1400K[77]	c-MET overexpression	SQ lung cancer First line+	Telisotuzumab Vedotin 2.7 mg/kg QD q3w	23	9[e] (0–20)	NR	2.4[e] (1.4–3.0)	5.6 (3.9–9.5)
MET exon 14-mutant								
GEOMETRY mono-1, NCT02414139 Phase II[70,78]	*MET*ex14 skipping mutation	Cohort 5b, First line	Capmatinib 400 mg BID	28	67.9 (47.6–84.1)	12.6 (5.6–NE)	12.4 (8.2–23.4)	20.8 (12.4–NE)
		Cohort 4, second/third line		69	40.6 (28.9–53.1)	9.7 (5.6–13.0)	5.4 (4.2–7.0)	13.6 (8.6–22.2)
		Expansion cohort 6, second line		31	51.6 (33.1–69.8)	8.4 (4.2–NE)	6.9 (4.2–13.3)	NE (13.5–NE)
		Expansion cohort 7, first line		32	65.6 (46.8–81.4)	NE (5.5–NE)	10.8 (6.9–NE)	NE (10.6–NE)
GeoMETry-III, NCT04427072 Phase III[79]	*MET*ex14 mutation	Second line+	Capmatinib 400 mg BID	15	53.3 (26.6–78.7)	9.9 (2.9–NE)	6.1 HR 0.46 (0.16–1.3) $p = 0.066$	NR
			Docetaxel 75 mg/m^2 q3w	7	0 (0–41.0)	NR	4.1	NR
CINC280J12201, NCT04323436 Phase II[79]	*MET*ex14 skipping mutation	First line Treatment naïve	Capmatinib 400 mg BID plus Spartalizumab 400 mg q4w	31	38.7[b] (21.8–57.8)	NYR	13.3[b] (9.3–NE)	NR
VISION, NCT02864992 Cohorts A and C Phase II[80,81]	*MET*ex14 skipping mutation	First line	Tepotinib 500 mg daily	164	57.3 (49.4–65.0)	46.4 (13.8–NE)	12.6 (9.7–17.7)	21.3 (14.2–25.9)
		Second line+	Tepotinib 500 mg daily	149	45.0 (36.8–53.3)	12.6 (9.5–18.5)	11.0 (8.2–13.7)	19.3 (15.6–22.3)
GLORY, NCT04270591 Phase I/II[82]	*MET*ex14 skipping mutation	First line+	Gumarontinib 300 mg QD	79	66 (54–76)	8.3 (6.3–NE)	8.5 (7.6–9.7)	17.3 (12.1–NE)
KUNPENG, NCT04258033 Phase II[83]	*MET*ex14 skipping mutation	First line+	Vebreltinib 200 mg BID q4w	52	75 (61.1–86.0)	15.9 (9.2–17.8)	14.1 (6.4–17.9)	20.7 (16.2–NE)
2016-504-00CH1, NCT02897479 Phase II[84,85]	*MET*ex14 skipping mutation	First line+	Savolitinib 400 or 600 mg daily	70	47.1 (35.1–59.5)	6.9 (4.9–12.5)	6.9 (4.6–8.3)	12.5 (10.5–21.4)

(Continued)

Table 2. (Continued)

Trial name, NCT# Phase	Molecular alteration	Line of therapy Pretreatment details	Regimen(s)	Patients, *n*	Overall response rate,[a] % (95% CI)	Median duration of response,[a] months (95% CI)	Median progression-free survival,[a] months HR (95% CI)	Median overall survival, months HR (95% CI)
CHRYSALIS, NCT02609776 Phase I[86]	*MET*ex14 mutation	First line+	Amivantamab 1050–1400 mg q1w ×4 then q2w	43	33.3[b] (18.6–51.0)	NYR[b] (2.1–12.2)	NR	NR
RET-rearranged								
ALL-RET, UMIN000020628 Phase I/II (expansion)[87]	*RET* fusion *EGFR* mutation and *ALK* rearrangement negative	Second line+ Prior CT, RET inhibitor-naïve	Alectinib 450 mg BID	25	4	NR	3.4 (2.0–5.4)	19 (5.4–NE)
LIBRETTO-001, NCT03157128 Phase II dose expansion[88,89]	*RET* fusion	First line	Selpercatinib 160 mg BID	69	84 (73–92)	20.2 (13.0–NE)	22.0 (13.8–NE)	NE
		Second line+ (prior platinum)	Selpercatinib 160 mg BID	247	61 (55–67)	28.6 (20.4–NE)	24.9 (19.3–NE)	NE
LIBRETTO-321, NCT04280081 Phase II[90]	*RET* fusion	First line+	Selpercatinib 160 mg BID	26	69.2 (48.2–85.7)	NYR	NYR	NYR
LIBRETTO-431, NCT04194944 Phase III[91]	*RET* fusion	First line	Selpercatinib 160 mg BID q3w	129	84 (76–90)	24.2 (17.9–NE)	24.8 (16.9–NE) HR 0.46 (0.31–0.70) $p < 0.001$	NYR HR 0.96 (0.50–1.83)
			Pemetrexed plus CT[f]	83	65 (54–75)	11.5 (9.7–23.3)	11.2 (8.8–16.8)	NYR
ARROW, NCT03037385 Phase I/II[92]	*RET* fusion	Cohort A, first line+	Pralsetinib 400 mg daily	28	72 (60–82)	NYR	NYR	NR
		Cohort B, second line (prior platinum)	Pralsetinib 400 mg daily	136	59[g] (50–67)	22.3 (15.1–NYR)	16.5 (10.5–24.1)	
BOS172738-01, NCT03780517 Phase I[93]	*RET* fusion	Second line+ (no alternative therapy approved)	BOS172738 10–150 mg daily	30	33[e]	NYR	NR	NR
KL400-I/II-01, NCT05265091 Phase I[94]	*RET* fusion	First line	KL590586 40–120 mg daily	25	76[e]	NYR	NR	NR
		Second line+ Prior anti-PD-1/PD-L1 therapy		32	63[e]	NYR	NR	NR
SY-5007-I, NCT05278364 Phase I[95]	*RET* fusion	Second line+ (previously treated)	SY-5007 20 mg daily or 20–200 mg BID	55	75.0[e] (53.3–90.2)	NR	NR	NR
HER2-altered								
2016-0783, NCT03066206 Phase II[96]	*HER2* exon 20 mutation	First line+	Poziotinib 16 mg daily q4w	30	27[b] (12–46)	5[b] (4.0–NE)	5.5[b] (4.0–7.0)	15 (9.0–NE)

(Continued)

Table 2. (Continued)

Trial name, NCT# Phase	Molecular alteration	Line of therapy Pretreatment details	Regimen(s)	Patients, *n*	Overall response rate,[a] % (95% CI)	Median duration of response,[a] months (95% CI)	Median progression-free survival,[a] months HR (95% CI)	Median overall survival, months HR (95% CI)
ZENITH20, NCT03318939 Phase II[97–99]	*HER2* exon 20 insertions	Cohort 2 Second line+	Poziotinib 16 mg daily	90	27.8 (18.9–38.2)	5.1 (4.2–5.5)	5.5 (3.9–5.8)	NR
		Cohort 4 First line	Poziotinib 16 mg daily	80	39 (28–50)	5.7 (4.6–11.9)	5.6 (5.4–7.3)	NR
ChiCTR1800020262 Phase II[100]	*HER2* exon 20 mutation (79.5%) *HER2* non-exon 20 mutation (20.5%)	First line+	Pyrotinib 400 mg daily	78	19.2[e] (11.2–30.0)	9.9[e] (6.2–13.6)	5.6[e] (2.8–8.4)	10.5 (8.7–12.3)
TRUMP, NCT03574402 Phase II (platform) HER2 cohort[101]	*HER2* mutation	First line	Pyrotinib 400 mg daily	28	35.7[b] (18.0–53.5)	6.4[b] (0.9–12.0)	7.3[b] (1.3–13.4)	14.3 (6.0–22.7)
PATHER2, ChiCTR1900021684 Phase II[102]	*HER2* mutation or amplification	Second line+ Prior anti-HER2/ TKI and/or CT	Pyrotinib 400 mg plus Apatinib 250 mg daily	33	51.5[b] (33.5–69.2)	6.0[b] (4.4–8.6)	6.9[b] (5.8–8.5)	14.8 (10.4–23.8)
21607, NCT05099172 Phase I[103]	*HER2* exon 20 insertions	Second line+	BAY2927088 q3w following a Bayesian adaptive dose-selection model	20	60[e,h]	NR	NR	NR
Beamion Lung 1, NCT04886804 Phase I[104,105]	*HER2* TKD mutations	Second line+	Zongertinib 30–300 mg QD	27	46[e]	NR	NR	NR
2021-FXY-191, NCT05016544 Phase Ib[106]	*HER2* mutation	NR	Inetetamab 8 mg/kg loading → 6 mg/kg plus Pyrotinib 320 mg daily	41	36.6[e]	NR	NR	NR
TAPUR, NCT02693535 Phase II (platform) HER2 cohort[107]	*HER2* mutation or amplification	First line+ Lung cancer of any histology (96.4% NSCLC)	Pertuzumab 840 mg loading dose then 420 mg q3w plus Trastuzumab 8 mg/kg loading dose then 6 mg/kg q3w	28	11[b] (2–28)	NR	3.7[b] (range: 2.1–5.3)[i]	NR
MyPathway, NCT02091141 Phase II (platform) HER2 cohort[108]	*HER2* amplified (43.2%)	Second line+	Pertuzumab 840 mg loading dose → 420 mg q3w plus Trastuzumab 8 mg/kg loading dose → 6 mg/kg q3w	16	13[b] (2–38)	7[b] (6–8)	2[b] (1–6)	NR
	HER2 mutated (56.8%)			21	19[b] (5–42)	9[b] (6–10)	4[b] (3–5)	NR
IFCT 1703-R2D2, NCT03845270 Phase II[109]	*HER2* mutation	Second line+ Progressed on platinum-based CT	Pertuzumab 840 mg loading dose → 420 mg q3w plus Trastuzumab 8 mg/kg loading dose → 6 mg/kg q3w	45	29[e] (17.8–40.0)	11[e] (2.9–14.9)	6.8[e] (4.0–8.5)	NR

(Continued)

Table 2. (Continued)

Trial name, NCT# Phase	Molecular alteration	Line of therapy Pretreatment details	Regimen(s)	Patients, *n*	Overall response rate,[a] % (95% CI)	Median duration of response,[a] months (95% CI)	Median progression-free survival,[a] months HR (95% CI)	Median overall survival, months HR (95% CI)
JapicCTI-194620 Phase II[110]	*HER2* exon 20 insertion mutation	Second line+ Prior CT	T-DM1 3.6 mg/kg q3w	21	38.1[e] (90%CI, 23.0–55.9)	3.5[e] (2.7–6.5)	2.8[e] (1.4–4.4)	8.1 (3.5–13.2)
TRAEMOS, NCT03784599 Phase I/II[111]	HER2 overexpression (IHC2+)	Second line+ Prior EGFR TKI	T-DM1 3.6 mg/kg q3w plus Osimertinib 80 mg QD	27	12 weeks ORR[e]: 4 (0–20)	NR	2.8[e] (1.4–4.6)	13.9 (10–16.9)
DESTINY-Lung01, NCT03505710 Phase II[112–114]	*HER2* alterations	Cohorts 1&2 Second line+	T-DXd 6.4 mg/kg q3w	91	55 (44–65)	9.3 (5.7–14.7)	8.2 (6.0–11.9)	17.8 (13.8–22.1)
	HER2 overexpression (IHC2+/3+)	Cohort 1 Second line+ Prior CT (92%) and PD-1/PD-L1 (73%)	T-DXd 6.4 mg/kg q3w	49	26.5 (15.0–41.1)	5.8 (4.3–NE)	5.7 (2.8–7.2)	12.4 (7.8–17.2)
		Cohort 1a Second line+ Prior CT (98%) and PD-1/PD-L1 (80%)	T-DXd 5.4 mg/kg q3w	41	34.1 (20.1–50.6)	6.2 (4.2–9.8)	6.7 (4.2–8.4)	11.2 (8.4–NE)
	HER2 mutation	Cohort 2 Second line+ Prior PD-1/PD-L1 (54.8%)	T-DXd 6.4 mg/kg q3w	42	61.9 (45.6–76.4)	NYR (5.3–NE)	14.0 (6.4–14.0)	NYR (11.8–NE)
DESTINY-Lung02, NCT04644237 Randomized phase II[115]	*HER2 mutation*	Second line+ (prior platinum)	T-DXd 5.4 mg/kg q3w	102	49.0 (39.0–59.1)	16.8 (6.4–NE)	9.9 (7.4–NE)	19.5 (13.6–NE)
			T-DXd 6.4 mg/kg q3w	50	56.0 (41.3–70.0)	NE (8.3–NE)	15.4 (8.3–NE)	NE (12.1–NE)
KRAS G12C(X)-Mutant								
CodeBreaK 100, NCT03600883 Phase II[116]	*KRAS* G12C mutation	Second line+ Prior PD-1/PD-L1 therapy (91.3%)	Sotorasib 960 mg daily	174	41 (33.3–48.4)	12.3 (7.1–15.0)	6.3 (5.3–8.2)	12.5 (10.0–17.8)
CodeBreaK 200, NCT04303780 Phase III[117]	*KRAS* G12C mutation	Second line+	Sotorasib 960 mg daily	171	28.1 (21.5–35.4) $p < 0.001$	8.6 (7.1–18.0)	5.6 (4.3–7.8) HR: 0.66 (0.51–0.86), $p = 0.0017$	10.6 (8.9–14.0) HR 1.01 (0.77–1.33), p = NS
			Docetaxel 75 mg/m^2 q3w	174	13.2 (8.6–19.2)	6.8 (4.3–8.3)	4.5 (3.0–5.7)	11.3 (9.0–14.9)
KRYSTAL-1, NCT03785249 Phase I/II[118]	*KRAS* G12C mutation	Second line+ Prior CT and PD-1/PD-L1 therapy	Adagrasib 600 mg BID	116	42.9 (33.5–52.6)	8.5 (6.2–13.8)	6.5 (4.7–8.4)	12.6[i] (9.2–19.2)
GO42144, NCT04449874 Phase Ia[119]	*KRAS* G12C mutation	Second line+	Divarasib 50–400 mg QD q3w	58	53.4[b] (39.9–66.7)	14.0[b] (8.3–NE)	13.1[b] (8.8–NE)	NR
D1553-102, NCT05383898 Phase I/II[120]	*KRAS* G12C mutation	Second line+	Garsorasib 600 mg BID	62	38.7[b] (26.6–51.9)	6.9[b] (5.4–NE)	7.6[b] (5.7–NE)	NR

(Continued)

Table 2. (Continued)

Trial name, NCT# Phase	Molecular alteration	Line of therapy Pretreatment details	Regimen(s)	Patients, *n*	Overall response rate,[a] % (95% CI)	Median duration of response,[a] months (95% CI)	Median progression-free survival,[a] months HR (95% CI)	Median overall survival, months HR (95% CI)
KontRASt-01, NCT04699188 Phase Ib/II[121]	*KRAS* G12C mutation	Second line+	JDQ443 monotherapy in dose escalation and food effect cohorts	24	41.7[e]	NR	NR	NR
CodeBreaK 100/101, NCT03600883/NCT04185883 Phase Ib-II[122]	*KRAS* G12C mutation	Second line+	Sotorasib 960 mg/day + Atezolizumab 1200 mg q3w or Pembrolizumab 200 mg q3w with or without lead-in Sotorasib 960 mg/day	58	29 (18–43)	17.9 (5.6–NE)	NR	15.7 (9.8–17.8)
CodeBreaK 101, NCT04185883 Phase Ib/II[123]	*KRAS* G12C mutation	Second-line+	Sotorasib 960 mg/day + RMC-4630 100/140/200 mg twice q1w	11	27[b] (6–61)	NR	NR	NR
NCT05288205 Phase I/IIa[124]	*KRAS* G12C mutation	Second line+ G12Ci naïve	Glecirasib plus JAB-3312	28	50[e]	NR	NR	NR
		KRAS G12Ci-pretreated		7	14.3[e]	NR	NR	NR
RAMP 202, NCT04620330 Phase II[125]	*KRAS* G12V mutation	Second line+	Avutometinib 4 mg BID	16	0	7.9	NR	NR
			Avutometinib 3.2 mg plus Defactinib 200 mg BID	19	11	8.5	NR	NR
SWOG S1507, NCT02642042 Phase II[126]	*KRAS* mutation	Second line+ Prior IO and/or CT	Trametinib 2 mg daily plus docetaxel 75 mg/m^2	53	34[e] (22–48)	5.0[e] (2.3–5.6)	4.1[e] (3.1–5.3)	10.9 (8.0–16.3)
KRYSTAL-7, NCT04613596 Phase II[127]	*KRAS* G12C mutation PD-L1 ⩾50%	First line	Adagrasib 400 mg BID plus Pembrolizumab 200 mg q3w	148	63	NYR (12.6–NE)	NYR (8.2–NE)	NR
SCARLET, jRCT2051210086 Phase II[128]	*KRAS* G12C mutation	First line, NSQ	Sotorasib 960 mg QD plus Carboplatin AUC5 and Pemetrexed 500 mg/m^2 q3w ×4	27	88.9 (80% CI: 78.5–94.8)	NR	NYR	6-mos OS: 87.0
RMC-6236-001, NCT05379985 Phase I[129]	*KRAS* G12X(non-C) mutation	Second line+	RMC-6236 80–400 mg daily	40	38[e]	NR	NR Median time on treatment: 3.1	NR

(Continued)

Table 2. (Continued)

Trial name, NCT# Phase	Molecular alteration	Line of therapy Pretreatment details	Regimen(s)	Patients, *n*	Overall response rate,[a] % (95% CI)	Median duration of response,[a] months (95% CI)	Median progression-free survival,[a] months HR (95% CI)	Median overall survival, months HR (95% CI)
FGFR-altered								
FIND, 2018-000399-13 Phase II[130]	*FGFR* alteration[k]	NR	Erdafitinib 3 mg–9 mg daily	22	9[e,h,l]	NR	NR	NR
NRG1-rearranged								
eNRGy, NCT02912949 Phase II[131]	*NRG1* fusion	First line+ (72% prior platinum)	Zenocutuzumab 750 mg q2w	40	37.2[b] (26.5–48.9)	14.9[b] (7.4–20.4)	NR	NR
PTK7-positive								
M19-611, NCT04189614 Phase Ib[132]	PTK7-expressing	Second line+ (all patients enrolled)	Cofetuzumab pelidotin 2.8 mg/kg q3w	56	19.6[e] (10.2–32.4)	7.2[e] (2.8–9.7)	5.3[e] (3.6–5.9)	NR
		NSQ EGFR WT, PTK7 ⩾90%/⩾2+ evaluable subset		20	30.0[e] (11.9–54.3)	5.8[e] (2.8–NE)	5.5[e] (2.6–8.5)	NR

Study inclusion criteria: Presented or published clinical trials of novel targeted therapy agents assessed in molecularly selected, alteration-drug-matched advanced/metastatic NSCLC. Trials reporting efficacy outcomes in the last 3 years and with ⩾20 NSCLC patients as well as select pivotal trials are included. Trials exclusively in the locally advanced setting were not included. This table serves as an update to Table 2 of our initial review on this topic[8]—studies included in that table were not included here unless their results were updated since the cutoff date for the previous review.

[a]By independent review unless otherwise specified.

[b]By investigator (local radiological) assessment.

[c]Based on the initial report of clinical activity in 26 ROS1+ patients enrolled in the respective study cohort.[48]

[d]With a 7-day lead-in period at 90 mg.

[e]Type of radiological assessment (by investigator or independent review) not specified.

[f]CT of investigator's choice with or without pembrolizumab 200 mg q3w.

[g]Includes two patients still on treatment with partial responses pending confirmation.

[h]Includes unconfirmed responses.

[i]Transformed from weeks to months using a conversion factor of 4.35 weeks/month.

[j]With an updated data cut-off date of January 15, 2022 (median follow-up of 15.6 months).

[k]Patients enrolled in three cohorts according to the type of alteration: High confidence activating FGFR translocations (1), high confidence activating FGFR mutations (2), and low confidence activating FGFR alterations (3).

[l]Both responses were observed in the cohort of patients with high confidence activating FGFR translocations. ORR in that cohort was 29%.

ALK, anaplastic lymphoma kinase; BID, twice daily; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CEP, centromere of chromosome 7; CI, confidence interval; c-Met, hepatocyte growth factor receptor; CT, chemotherapy; DoR, duration of response; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GCN, gene copy number; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HRG, heregulin; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, hepatocyte growth factor receptor; mos, months; *n*, number; NCT, national clinical trial; NE, not estimable; NR, not reported; NRG1, neuregulin-1; NS, non-significant; NSCLC, non-small-cell lung cancer; NSQ, non-squamous cell; NTRK, neurotrophic tyrosine receptor kinase; NYR, not yet reached; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PTK7, tyrosine-protein kinase-like 7; QD, once daily; qXw, every X weeks; R2PD, recommended phase II dose; RET, rearranged during transfection; ROS1, c-ros oncogene 1; SQ, squamous cell; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor; WT, wild-type; #th line+, #th line of treatment in the advanced setting or higher.

from 174 clinical trials or integrated analyses reporting efficacy outcomes on novel oncogene-directed therapies in alteration-matched advanced NSCLC (PRISMA, Figure 1). Study analyses were grouped by molecular target and will be discussed chronologically based on the availability of a Food and Drug Administration (FDA) approved agent: *c-ros oncogene 1 (ROS1)*-rearranged ($n = 23$), v-*Raf murine sarcoma viral oncogene homolog B1 (BRAF) V600*-mutated ($n = 9$), *neurotrophic tyrosine receptor kinase (NTRK)*-rearranged ($n = 4$), *hepatocyte growth factor receptor (MET)*-altered ($n = 35$), *rearranged during transfection (RET)*-rearranged ($n = 15$), *human epidermal growth factor receptor (HER)2*-altered ($n = 38$), *Kirsten rat sarcoma viral oncogene homolog (KRAS)*-mutated ($n = 32$), *fibroblast growth factor receptor (FGFR)*-altered ($n = 10$), *HER3-/neuregulin-1 (NRG1)*-altered ($n = 10$), *phosphoinositide 3-kinase (PI3K)*-altered ($n = 2$), and *tyrosine-protein kinase-like 7 (PTK7)*-mutated ($n = 1$). Analyses with ⩾20 NSCLC biomarker-selected patients reporting outcomes in the last 3 years (since September 2020) are summarized in Table 2 ($n = 73$).

ROS1-*rearranged*

The ROS1 tyrosine kinase domain shares 84% and 86% sequence similarity with ALK and tropomyosin receptor kinase (TRK), respectively.[133,134] Consequently, two main types of inhibitors have been assessed in patients with tyrosine kinase inhibitor (TKI)-naïve and -pretreated NSCLC harboring *ROS1* rearrangements: those that co-inhibit ALK/ROS1[53,135–146] and those that co-inhibit TRK/ROS1.[144–147] In TKI-naïve patients, the ALK/ROS1/MET co-inhibitor crizotinib was the first agent to receive regulatory approval for NSCLC with *ROS1* rearrangements in 2016 based on results from the phase I PROFILE-1001 study.[148] Updated results confirmed initial findings of frequent (objective response rate (ORR) 72%) and durable (median duration of response (mDoR) 24.7 months) responses and showed strong median progression-free survival (mPFS 19.3 months) and median overall survival (mOS 51.4 months) outcomes.[141] Multiple other phase I–II studies of crizotinib in ROS1-rearranged NSCLC have confirmed its clinical efficacy[45,46,48,50,140] and updated results from three of these studies demonstrated robust survival outcomes with mPFS of 13.8–19.4 months and mOS of 40.5–54.8 months at a median follow-up of 54.4–81.4 months[45,47,49,50] (Table 2). With few exceptions where ORRs were modest (ensartinib 27%, iruplinalkib 36.8%),[55,138] other ALK/ROS1 inhibitors (ceritinib, lorlatinib, brigatinib, and unecritinib) have shown high clinical activity as initial ROS1-directed therapy (ORR 62%–80.2%),[53,54,136,142,143] however have yet to receive regulatory approval for *ROS1*-rearranged NSCLC. In particular, unecritinib (a novel derivative of crizotinib) was recently associated with an 80.2% ORR, 20.3-month mDoR, and mPFS of 16.5 months.[53]

Entrectinib is a brain-penetrant agent and was the first TRK/ROS1 inhibitor to receive accelerated approval for TKI-naïve *ROS1*-rearranged NSCLC based on results from an NSCLC-specific integrated analysis of phase I–II studies in multiple tumors.[149] At a median follow-up of 29.1 months, entrectinib continued to show frequent and durable responses (ORR 67.9%; mDoR 20.5 months), with a mPFS and mOS of 15.7 and 47.8 months, respectively.[52] Taletrectinib and repotrectinib are potent, next-generation TRK/ROS1 inhibitors designed to improve central nervous system activity and overcome treatment resistance with favorable safety profiles that showed early signs of activity in *ROS1*-rearranged NSCLC.[146,147,150] Treatment with repotrectinib resulted in frequent and durable responses and robust PFS in the ROS1-TKI-naïve cohort of the phase II trial TRIDENT-1 (ORR 79%; mDoR 34.1 months; mPFS 35.7 months),[56,144] leading to a priority review designation[151] and subsequent approval by the FDA.[152] After displaying promising activity in phase I studies,[147,153] taletrectinib showed the highest response rates across studies of ROS1 inhibitors in the phase II trials TRUST and TRUST-II (92.5% and 92.0%),[57,58,145] leading to a breakthrough therapy designation by the FDA.[154]

Since the seminal approval of crizotinib, several studies have assessed the clinical activity of ROS1 inhibitors, in ROS1-TKI-pretreated patients. The ALK/ROS1 inhibitors, lorlatinib and brigatinib, were among the first to demonstrate activity in this setting with ORRs between 26.3% and 35%.[135,143,155] In a small study of patients with brain-only progression while on crizotinib, lorlatinib (an agent designed specifically to penetrate the blood–brain barrier)[156] led to an ORR of 67% at 12 weeks and 87% while on the study.[137] Recently, the next-generation TRK/ROS1 inhibitors, repotrectinib and taletrectinib, have also shown promise. Repotrectinib received

FDA approval in this setting based on an ORR of 38% and a mDoR of 14.8 months in the cohort of ROS1-TKI-pretreated patients from TRIDENT-1[144,56,152] and taletrectinib demonstrated impressive ORRs of 52.6% and 57.1% in the cohorts of ROS1-TKI-pretreated patients from TRUST and TRUST-II.[57,58,145,146] NVL-520, a ROS1-selective inhibitor designed to avoid neurotoxicity associated with TRK inhibition, showed promising clinical activity (ORR 48%) in a heavily pretreated population, including at least one prior ROS1-inhibitor, displaying both brain penetration and activity against resistance mutations.[59]

In summary, both ALK/ROS1 and TRK/ROS1 inhibitors are highly active and have been approved for the treatment of NSCLC with *ROS1* rearrangements; more potent and selective next-generation inhibitors continue to improve clinical efficacy and safety leading to additional regulatory approvals.

BRAF-V600-*mutant*

In contrast with *ROS1*-altered and other oncogene-driven NSCLCs (see below), high clinical activity in *BRAF-V600*-mutated NSCLC was only achieved thus far with a combination of both direct and downstream inhibition with BRAF[60,63–65,108,157–161] and mitogen-activated protein kinase kinase (MEK)1/2 inhibitors.[60,63–65,161,162] Similar to the targeting of *BRAF* mutations in melanoma, the use of these inhibitors as monotherapy (namely selumetinib or vemurafenib) produced minimal to modest clinical activity in NSCLC[108,158,159,162] leading to combination therapy trials. The first combination to be approved was the BRAF inhibitor dabrafenib plus the MEK1/2 inhibitor trametinib for *BRAF-V600E*-mutated NSCLC based on outcomes from the phase II BRF113928 trial.[61,62,163] At a median follow-up of 16.3–16.6 months, initial findings in both treatment-naïve and pretreated cohorts were confirmed with frequent and durable responses (ORR 63.9% and 68.4%; mDoR 10.2 and 9.8 months, respectively) and robust mPFS (10.8 and 10.2 months) and OS outcomes (17.3 and 18.2 months; Table 2).[60] The clinical activity of dabrafenib plus trametinib in this setting is also supported by an ORR of 75% from a recent phase II trial.[63]

Two additional inhibitor combinations were developed to increase the potency, selectivity, and safety of at least one of the combination partners relative to prior BRAF and/or MEK inhibitors.[30,164,165] The PHAROS phase II study demonstrated good activity for the second-generation combination of encorafenib plus binimetinib in treatment-naïve and pretreated cohorts (ORRs of 75% and 46%, respectively), durable responses (mDoR not yet reached (NYR) and 16.7 months), and robust mPFS (NYR and 9.3 months).[64] These findings supported approval of encorafenib plus binimetinib for the treatment of metastatic *BRAF-V600E* NSCLC on October 2023.[166] Recently, the HL-085-102 trial reported favorable outcomes for vemurafenib plus the highly potent and selective MEK inhibitor tunlametinib in pretreated NSCLC patients with *BRAF-V600* mutations (ORR 60.6%, mDoR 11.3 months, mPFS 11.7 months).[65] Other BRAF inhibitor combinations have been tested in this setting with no breakthrough results to date.[157,160,161]

The development of BRAF and MEK inhibitor combinations continues to evolve with next-generation agents. A promising approach currently in early clinical testing is the use of BRAF dimer inhibitors (belvarafenib, DCC-3084, BGB-3245, PF-07799933)[161,167–169] which prevent the paradoxical activation of MAPK signaling leading to resistance observed with BRAF monomer inhibitors and the need for a MEK inhibitor. These new agents are also active against Class II and III BRAF mutations.[170,171]

NTRK-*rearranged*

Inhibitors of TRK-A/B/C have been assessed in *NTRK*-rearranged solid tumors including the first-generation agents larotrectinib[66,172] and entrectinib[67,173] and the next-generation TRK inhibitors taletrectinib[146] and repotrectinib.[68,174] Both larotrectinib and entrectinib were approved in 2018 and 2019, respectively, for tumor-agnostic indications in *NTRK* fusion-positive tumors based on integrated analyses of multicenter, single-arm trials.[149,175] Up-to-date, tumor-agnostic and tumor-specific analyses have generally confirmed the benefit of these agents in lung cancer. Integrated analysis of phase I/II LOXO-TRK-14001, NAVIGATE, and SCOUT trials reported an ORR of 69% and mDoR, mPFS, and mOS of 32.9, 29.4, and NYR months for larotrectinib among 269 patients with solid tumors and an ORR of 73%, mDoR, mPFS, and mOS of 33.9, 35.4, and 40.7 months, respectively, among a subgroup of 20 lung cancer patients[66] (Table 2).

Similar analyses of the phase I/II STARTRK-2, STARTRK-1, and ALKA-372-001 studies evaluating entrectinib reported an ORR of 62.4% and mDoR, mPFS, and mOS of 29.4, 15.7, and 38.2 months among 194 patients with solid tumors[173] and an ORR of 62.7% and mDoR, mPFS, and mOS of 27.3, 28.0, and 41.5 months among 51 patients with NSCLC.[67]

The next-generation TRK inhibitor repotrectinib has also demonstrated clinical activity in patients with *NTRK*-rearranged solid tumors,[174] leading to a breakthrough therapy designation by the FDA in October 2021.[176] In a recent update of the TRIDENT-1 basket trial, repotrectinib continued to show promising clinical activity in solid tumors with ORRs of 58% and 50% in TKI-naïve and -pretreated cohorts and of 62% and 42% in the respective subsets of NSCLC patients.[68]

TRK inhibitors have shown strong activity and robust clinical outcomes across different *NTRK*-fusion positive tumors including NSCLC, representing one of the most compelling examples of alteration-drug matching.

MET-*altered*

A host of agents have been assessed in *MET*-altered NSCLC including nonselective MET inhibitors (crizotinib[48,69,140,177–182] and S49076[183]), selective MET inhibitors (capmatinib,[70,72,78,79,184,185] tepotinib,[71,80,81] savolitinib,[84,85,186,187] glumetinib,[188,189] bozitinib,[190] ABN401,[191] SAR125844,[192] vebreltinib,[83] and gumarontinib[82]), dual MET/X inhibitors (glesatinib,[73] BPI-9016M,[74] and OMO-1[193]), anti-MET antibodies (onartuzumab[194] and emibetuzumab[195]), antibody mixtures (Sym015-01[196]), bispecific METxEGFR (amivantamab,[86] CKD-702[197]) and METxMET (REGN5093[75]) antibodies, and anti-MET antibody–drug conjugates (ADCs; telisotuzumab vedotin[76,77,198]). Multiple biomarkers and thresholds have also been used to select patients with variable clinical activity across studies with different agents and biomarker selection criteria.

MET-*amplified or -overexpressed.* In patients selected exclusively based on *MET* amplification, the multi-targeted-TKI crizotinib and the selective MET inhibitor capmatinib are the most well-studied agents and have generally shown only limited to modest clinical activity with an apparent relationship between higher *MET* amplification and improved outcomes in some studies.[48,69,70,140,177,179,184] Other selective MET inhibitors have also shown preliminary efficacy signals in patients with *MET*-amplified tumors.[71,184,192]

Multiple MET inhibitors have been assessed in patients with MET overexpression or a variety of *MET* alterations. The first-in-class ADC telisotuzumab vedotin failed to meet the pre-specified response criteria for continuing enrolment in the subprotocol S1400K of Lung-MAP with an ORR of 9%[77] and displayed only modest activity in the LUMINOSITY phase II trial (ORR 22.1%).[76] Interestingly, biomarker analyses from LUMINOSITY revealed higher ORR in nonsquamous NSCLC without EGFR mutations and high MET overexpression (⩾50% by immunohistochemistry; ORR 52.2%).[76] Studies assessing small-molecule inhibitors or antibody-based agents with dual or bispecific targeting showed limited to modest activity (ORRs 2.6%–25.9%).[73–75,196]

MET*ex14-mutant.* Studies of MET inhibitors in patients with NSCLC harboring predominantly *MET*ex14 mutations generally resulted in more favorable clinical outcomes than those seen in *MET*-amplified/-overexpressed NSCLC.[140,70,81,177,180,186,187] Crizotinib demonstrated variable activity in *MET*ex14 NSCLC (ORR 12%–65%),[57,177,179–181] and received an FDA breakthrough therapy designation in 2018[199] based on favorable results from the PROFILE-1001 study.[182] The first regulatory approval in this setting was granted to the selective MET inhibitor capmatinib based on results from the multi-cohort GEOMETRY mono-1 phase II trial.[200] Updated results from this study showed frequent and durable responses and robust PFS and OS outcomes in both treatment-naïve (ORR 65.6%–67.9%, mDoR 12.6–NYR months, mPFS 10.8–12.4 months, mOS 20.8–NYR months in initial and expansion cohorts) and previously treated patients (ORR 40.6%–51.6%, mDoR 8.4–9.7 months, mPFS 5.4–6.9 months, mOS 13.6–NYR months in initial and expansion cohorts).[70,78] More recently, the GeoMETry-III phase III trial comparing capmatinib to standard-of-care docetaxel in previously treated *MET*ex14 NSCLC showed numerical differences in ORR (53.3% vs 0%) and PFS (6.1 vs 4.1 months; hazard ratio (HR) 0.46, 95% confidence interval (CI) 0.16–1.3, $p = 0.066$) that although consistent with GEOMETRY mono-1 results did not reach statistical significance after early trial

termination.[79] Tepotinib was the second selective MET inhibitor to receive accelerated approval for *MET*ex14 NSCLC in February 2021 based on initial results from the large phase II VISION trial.[201] Updated results confirmed initial findings with frequent and durable responses and robust PFS and OS outcomes in both treatment-naïve and pretreated patients (ORR 57.3% and 45.0%, mDoR 46.4 and 12.6 months, mPFS 12.6 and 11.0 months, mOS 21.3 and 19.3 months, respectively).[80] Additional selective MET inhibitors have also shown preliminary efficacy signals[187,189–191] that were confirmed in larger cohorts of phase II studies of savolitinib, gumarontinib, and vebreltinib (ORRs 47.1%, 66%, and 75%, respectively).[82–86] Notably, vebreltinib showed high activity, durable responses, and robust PFS outcomes in both treatment-naïve and pretreated cohorts of the KUNPENG study (ORR 77.1% and 70.6%; mDoR 16.5 and 15.3 months; mPFS 14.5 and 7.1 months).[83] The dual MET/OCT-2 inhibitor OMO-1 and the bispecific METxEGFR antibody CKD-702 have shown early signs of activity.[193,197] The combination of capmatinib with the immune checkpoint inhibitor (ICI) spartalizumab was assessed in treatment-naïve patients resulting in a modest ORR (38.7%) and high rates of treatment-related adverse events prompting early trial termination.[185]

In crizotinib-pretreated patients with predominantly skipping alterations (75%), capmatinib showed minimal activity (ORR 10%)[72] while in MET-inhibitor-pretreated patients, the bispecific METxEGFR antibody amivantamab demonstrated promising clinical activity (ORR 33%) in the *MET*ex14 cohort of the CHRYSALIS phase I trial.[86]

In summary, targeting *MET* dysregulation with MET inhibitors has been successful in *MET*ex14 NSCLC. More potent and selective next-generation TKIs have shown high clinical activity and are the only type of agents approved thus far in this setting. In *MET*-amplified/-overexpressed tumors, encouraging results have been observed particularly in *MET*-amplified subsets. An interesting relationship between levels of MET enrichment and clinical activity was apparent in multiple studies.

RET-*rearranged*

Earlier generation multi-kinase inhibitors (cabozantinib, alectinib, vandetanib, lenvatinib, and ponatinib)[87,202–208] and more selective RET TKIs (selpercatinib, pralsetinib, BOS172738, KL590586, SY-5007)[88–95,209] have been assessed in patients with NSCLC harboring *RET* rearrangements. Small phase I–II trials (⩽25 patients) assessing multitargeted TKIs for which RET is a secondary target generally reported minimal activity (ORRs 4%–28%)[87,202,203,205,207] except the LURET phase II trial of vandetanib which reported a promising ORR of 53%.[204,208] More recently, studies of selective RET TKIs have demonstrated improved outcomes. Selpercatinib was the first agent approved by the FDA in this setting[210] based on initial results of the large, multi-cohort non-randomized LIBRETTO-001 phase II trial.[89] Trial results were recently confirmed showing frequent and durable responses and robust PFS outcomes in both treatment-naïve (ORR 84%, mDoR 20.2 months, mPFS 22.0 months) and pretreated patients (ORR 61%, mDoR 28.6 months, mPFS 24.9 months; Table 2).[88] The smaller phase II trial LIBRETTO-321 further confirmed the favorable clinical activity of selpercatinib in patients with *RET*-rearranged NSCLC with an ORR of 69.2% (87.5% in treatment-naïve and 61.1% in pre-treated subsets).[90] Recently, the phase III trial LIBRETTO-431 comparing selpercatinib to chemotherapy as initial treatment of *RET*-rearranged NSCLC met its primary endpoint with a large improvement in mPFS (24.8 vs 11.2 months; HR 0.46, $p < 0.001$) and more frequent and longer responses (ORR 84% vs 65%; mDoR 24.2 vs 11.5 months) for selpercatinib.[91] In September 2022, selpercatinib received full FDA approval for *RET*-rearranged NSCLC based on the updated results from the NSCLC cohort of the LIBRETTO-001 trial.[211] The FDA has also granted full approval to pralsetinib for the treatment of *RET* fusion-positive NSCLC in August 2023[212] based on the recently updated results of the phase II ARROW trial which confirmed initial findings[209] with an ORR of 72% and mDoR NYR among chemotherapy-naïve patients and ORR of 59% and mDoR of 22.3 months among platinum-pretreated patients.[92] Median PFS was NYR and 16.3 months in chemotherapy-naïve and -pretreated patients, respectively. Other highly potent and selective RET inhibitors (BOS172738, KL590586, and SY-5007) have shown promising clinical activity in phase I trials (ORR 33%–76%).[93–95] Similar to other alteration-matched settings, selective RET TKIs have improved outcomes relative to multitargeted

TKIs in the treatment of *RET*-arranged NSCLC; selpercatinib and pralsetinib are the only agents approved in this setting.

HER2-*altered*

Four main types of inhibitors, dual- or pan-HER TKIs (BAY2927088, neratinib, dacomitinib, afatinib, pyrotinib, poziotinib, and tarloxotinib-effector),[96–103,213–221] selective HER2 TKIs (zongertinib),[104,105,222] anti-HER2 monoclonal antibodies (mAbs; trastuzumab, pertuzumab, and inetetamab),[106–109,223–227] and anti-HER2 ADCs (ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd))[110–115,228–232] have been assessed in patients with NSCLC with *HER2* alterations.

Second-generation small-molecule TKIs that were primarily developed as EGFR inhibitors in NSCLC (dacomitinib, afatinib, and neratinib) were tested in *HER2*-altered NSCLC showing limited activity as single agents (ORRs 0%–12%).[213,215,216,218,219] More recently, newer next-generation multi-HER TKIs (poziotinib, pyrotinib, tarloxotinib, BAY2927088, BDTX-189) and HER2-selective TKIs (zongertinib) have shown better yet generally modest activity in primarily *HER2*ex20-mutated NSCLC (ORR 19.2%–60%; Table 2).[96–105,214,220–222] Of these, the highest ORR was observed with the multi-HER TKI BAY2927088 (60%)[103] leading to an FDA breakthrough designation for HER2-mutated NSCLC.[223] No small-molecule HER2 TKI has been approved to date for the treatment of *HER2*-altered NSCLC.

Antibody-based agents have the potential to increase selectivity and specificity relative to multitargeted TKIs. However, the use of single or dual anti-HER2 mAb regimens with or without chemotherapy has resulted in minimal to modest activity in HER2-altered NSCLC (0%–45%; Table 2).[106–109,224–228] Recently, two ADCs, T-DM1 and T-DXd, have been prospectively assessed in this setting. T-DM1, which delivers a microtubule-inhibitory payload to HER2-presenting cells, has shown minimal activity in patients with pretreated *HER2*-amplified/-overexpressed NSCLC (ORR 6.7%–20%)[229–231] and moderate activity in chemotherapy-pretreated patients with HER2ex20 insertions (ORR 38.1%).[110] T-DM1 also showed limited activity when combined with osimertinib in osimertinib-pretreated patients with HER2 overexpression.[111] T-DXd, which delivers a topoisomerase 1 inhibitor payload, has shown greater activity overall in *HER2*-altered (including overexpressed and mutated) NSCLC with ORRs of 55.6% and 55% in heavily pretreated patients from a phase I study dose-expansion cohort and the phase II DESTINY-Lung01 trial, respectively.[113,114,232] Both studies reported high ORRs in patients with *HER2* mutations compared with HER2 overexpression (72.7% and 61.9% vs 26.5%–34.1%, respectively).[112,113,232] Longer mDoR, mPFS, and mOS in HER2-mutated relative to HER2-overexpressed patients were also apparent in DESTINY-Lung01 (NYR vs 5.8–6.2 months, 14.0 vs 5.7–6.7 months, and NYR vs 11.2–12.4 months, respectively). T-DXd received a breakthrough therapy designation for use in platinum-pretreated *HER2*-mutant NSCLC patients from the FDA in May 2020 based on results of DESTINY-Lung01.[233] More recently, results from the randomized phase II trial DESTINY-Lung2 comparing two doses of T-DXd (5.4 vs 6.4 mg/kg every 3 weeks (q3w)), confirmed the favorable outcomes (ORR 49.0% and 56.0%; mDoR 16.8 months and NYR; mPFS 9.9 and 15.4 months; mOS 19.5 months and NYR for the 5.4 and 6.4 mg/kg q3w doses, respectively)[115] leading to the FDA granting only the lower-dose regimen accelerated approval for use in *HER2*-mutant NSCLC in August 2022 due to concerns of higher rates of interstitial lung disease/pneumonitis with 6.4 mg/kg q3w.[234] This regimen is also being evaluated for a HER2-amplified, tumor-agnostic indication with promising efficacy.[235] Other HER2-directed ADCs (A166 and ARX788) and bispecific antibodies (KN026) have shown promising results in early-phase studies in *HER2*-altered tumors; however, their efficacy in NSCLC has yet to be established.[236–238]

Several clinical studies now show a greater benefit for HER2-directed therapy in those with HER2 mutations compared to other types of HER2 alterations, with the best outcomes observed for the ADC T-DXd which was approved for HER2-mutated NSCLC.

KRAS-*mutant*

Multiple approaches have sought to target *KRAS* mutations in NSCLC, including direct inhibition with RAS/RAF blockers[125,239,240] and indirect approaches such as inhibition of downstream effectors,[125,126,240–251] cyclin-dependent kinases 4/6,[252–254] and other targets.[125,242,247,249,250,255] The

first successful effort to directly target KRAS in NSCLC emerged from the development of agents that selectively and irreversibly bind and stabilize the KRAS-G12C inactive form (single-OFF KRAS-G12C inhibitors).[118,256–259] Sotorasib and adagrasib received accelerated approval from the FDA in May 2021 and December 2022[260,261] for previously treated, *KRAS*-G12C-mutant NSCLC based on results from the multicenter, single-arm trials CodeBreaK100 and KRYSTAL-1, respectively.[118,258] Initial results from CodeBreaK100 were confirmed in a 2-year update showing frequent and durable responses and robust time-to-event outcomes (ORR of 41% and mDoR, mPFS, and mOS of 12.3, 6.3, and 12.5 months, respectively).[116] After a median follow-up of 17.7 months, the confirmatory, phase III trial CodeBreaK200 met its primary endpoint of PFS (median 5.6 vs 4.5 months, HR 0.66, $p = 0.0017$) and showed significant improvement in ORR (28.1% vs 13.2%, $p < 0.001$) with sotorasib relative to docetaxel in platinum-pretreated patients.[117] However, benefits in mDoR (8.6 months (95% CI 7.1–18.0) vs 6.8 months (95% CI 4.3–8.3)) and OS (10.6 vs 11.3 months, $p = 0.53$) were not apparent which may be in part due to removal of OS as a co-primary endpoint, consequent reduction in sample size and introduction of crossover from docetaxel to sotorasib in a trial amendment.[262] Despite CodeBreaK200 meeting its primary endpoint, the FDA ruled that the primary endpoint data could not be reliably interpreted and postponed conversion to full approval.[263] Initial results from the KRYSTAL-1 trial leading to accelerated approval of adagrasib were comparable to sotorasib's registrational data with an ORR of 42.9% and mDoR, mPFS, and mOS of 8.5, 6.5, and 12.6 months, respectively.[118] Adagrasib's confirmatory trial KRYSTAL-12 is ongoing. More recently, the new potent and selective G12C inhibitors divarasib, JDQ443, and garsorasib have shown promising activity as single agents with ORRs of 53.4%, 41.7%, and 38.7%, mDoR of 14.0, not reported (NR) and 6.9 months, and mPFS of 13.1, NR and 7.6 months, respectively.[119–121] Additional single-OFF G12C inhibitors are either in very early stages of clinical development or have been halted due to safety and/or efficacy concerns.[264–268]

New RAS inhibitors are now being developed toward different individual mutations (*KRAS*-G12X) or with a wider selectivity range (from multi-KRAS to multi-RAS), and targeting active (ON) forms.[259] Recently, the first-in-class, RAS-selective, tri-complex multi-ON RAS inhibitor, RMC-6236, showed promising preliminary clinical activity in *KRAS*-G12X(D/V/A/S/R) NSCLC (ORR 38%; Table 2).[129]

Data on combination regimens in patients with *KRAS*-G12C mutations have recently emerged. Combination of sotorasib with ICIs (atezolizumab or pembrolizumab) showed only moderate activity (ORR 29%) in cohorts of the CodeBreak100/101 trials where frequent grade 3/4 hepatotoxicity limited ability to maintain dosing.[122] Higher ORRs were observed with the selective KRAS-G12C inhibitors MK-1084 and adagrasib in combination with pembrolizumab (47% and 63%, respectively) in programmed death-ligand 1 (PD-L1)-positive (tumor proportion score (TPS) $\geqslant$1%) and PD-L1-high (TPS $\geqslant$ 50%) patients, respectively.[127,269] Combinations of sotorasib or glecirasib with SHP2 inhibitors (RMC4630 or JAB-3312, respectively) in pretreated patients showed moderate ORRs overall (43% and 27%, respectively) with promising activity in G12C inhibitor-naïve subsets (ORR of 50% in both studies).[123,124] Combinations of MEK inhibitors (binimetinib, trametinib, or avutometinib) with other systemic agents (chemotherapy, defactinib, or multi-TKIs (erlotinib, anlotinib, ponatinib)) have shown variable activity in pretreated patients with *KRAS* mutations (ORRs 0%–60%).[125,126,242,243,246–249] In chemotherapy-naïve non-squamous NSCLC patients, first-line sotorasib plus carboplatin-pemetrexed showed an impressive ORR of 88.9% and PFS and OS rate at 6 months of 81.2% and 87.0% in the SCARLET phase II trial.[128]

In summary, the development of agents that indirectly target KRAS (such as MEK/ERK inhibitors) has not been successful in *KRAS*-mutant NSCLC. KRAS-G12C single-OFF inhibitors have shown strong activity in previously treated, *KRAS*-G12C-mutant NSCLC and are the only type of targeted agents approved in this setting. New single- and multi-ON inhibitors are promising agents as they can more directly inhibit active RAS forms and have the potential to simultaneously inhibit different aberrant forms; however, these are still in very early stages of development.

Other targets

Several targeted therapies are being developed in alteration-drug-matched settings without a

first-in-class regulatory approval to date, including *FGFR*-, *HER3*-, *NRG1*-, *PTK7*-, and *PI3K*-altered NSCLC.

FGFR inhibition of *FGFR*-altered NSCLC was initially attempted with non-selective inhibitors mostly in *FGFR*-amplified/overexpressed tumors resulting in considerable toxicity with minimal activity.[270–273] The use of FGFR-selective, multi- or pan-FGFR inhibitors eased safety concerns; however, clinical activity remained minimal (ORRs 4%–11%).[274–277] The recently presented results of the FIND and RAGNAR trials of erdafitinib followed this trend with minimal to modest activity in NSCLC patients with *FGFR* alterations (ORRs of 9% and 26%, respectively).[130,278] Moreover, rogaratinib treatment of squamous NSCLC with *FGFR* alterations produced no responses in SAKK19/18 which was closed prematurely due to futility.[279]

In addition to inhibition of *HER2*-altered NSCLC, multiple approaches have sought to address aberrant HER signaling, including anti-HER3 mAbs and small-molecule pan-HER inhibitors in patients with HER3 or NRG1 overexpression/amplification or *NRG1* rearrangements. Testing of small-molecule pan-HER inhibitors in *HER1-3*-altered NSCLC had limited success.[280–282] Although circulating NRG1 levels were initially identified as potentially predictive of efficacy of the anti-HER3 mAb patritumab plus erlotinib in the randomized phase II HERALD trial,[283] the phase III HER3-Lung study failed to confirm this finding.[284] Similarly, the addition of the anti-HER3 mAbs lumretuzumab or seribantumab to either chemotherapy or EGFR inhibitors did not show meaningful benefit (ORRs of 6.3% and 19.7% in pretreated patients and 42.9% in a small subset of chemotherapy-naïve patients) despite early signals of higher activity in HER3- or NRG1-enriched NSCLC.[285–288] The anti-HER3 mAb GSK2849330 showed minimal activity in HER3-expressing cancers ($n = 29$) with a single yet durable response in an NSCLC patient with a *cluster of differentiation 74-NRG1* rearrangement.[289] When *NRG1* rearrangements were used as biomarker selection criteria, seribantumab and the HER2/HER3 bispecific antibody zenocutuzumab showed moderate yet promising activity with durable responses in previously treated NSCLC patients enrolled in the CRESTONE (ORR 36%)[290] and eNRGy trials (ORR 37.2%; mDoR 14.9 months).[131] These agents have received fast-track or priority review designations from the FDA in *NRG1*-rearranged tumor-agnostic or NSCLC-specific indications.[291,292]

Development of therapies targeted to PI3K and PTK7 in the respective biomarker alteration-matched NSCLC populations is in the very early stages of development without a clear breakthrough to date.[132,293,294]

Discussion

Development of therapies directed toward driver genes in molecularly selected, advanced NSCLC is an extremely active research field with a large number of studies evaluating new agents in previously identified targets (particularly in *MET*-, *HER2*-, and *KRAS*-altered disease) and new potentially actionable molecular targets (NRG1 and PTK7). *MET*, *HER2*, *KRAS*, *ROS1*, *RET*, and *BRAF* alterations are both clinically actionable and relatively common in NSCLC patients (>1%). It is therefore not surprising that these are among the most studied populations. Although *NTRK* alterations are uncommon (⩽1%), their clinical actionability has been convincingly demonstrated independent of tumor type, with high clinical activity across multiple tumors and several tumor-agnostic approvals.

The number of unique clinically actionable settings defined by oncogenic alterations (other than those of *EGFR* and *ALK*) continues to grow and clinical research efforts in this field have led to a large number of FDA approvals in the last 3 years ($n = 9$).[295] Many of these are in patient populations with a high clinical need as oncogenic alterations tend toward more aggressive cancers with few treatment options. The clinical impact of alteration-matched therapies is also reflected in trial eligibility for new non-oncogenic-targeted agents (such as ICIs) which now often exclude patients with clinically actionable alterations (*EGFR*, *ALK*, *ROS1*, and others). Moreover, approval of tumor-agnostic indications for the same alteration-drug pairs previously approved in NSCLC[296,297] serves as further validation of the applicability of this strategy. However, despite efforts to standardize reporting and interpretation of alteration-drug-matched clinical trial data,[298–302] regulatory approvals and reimbursement vary across regions limiting access in certain jurisdictions.[303–308]

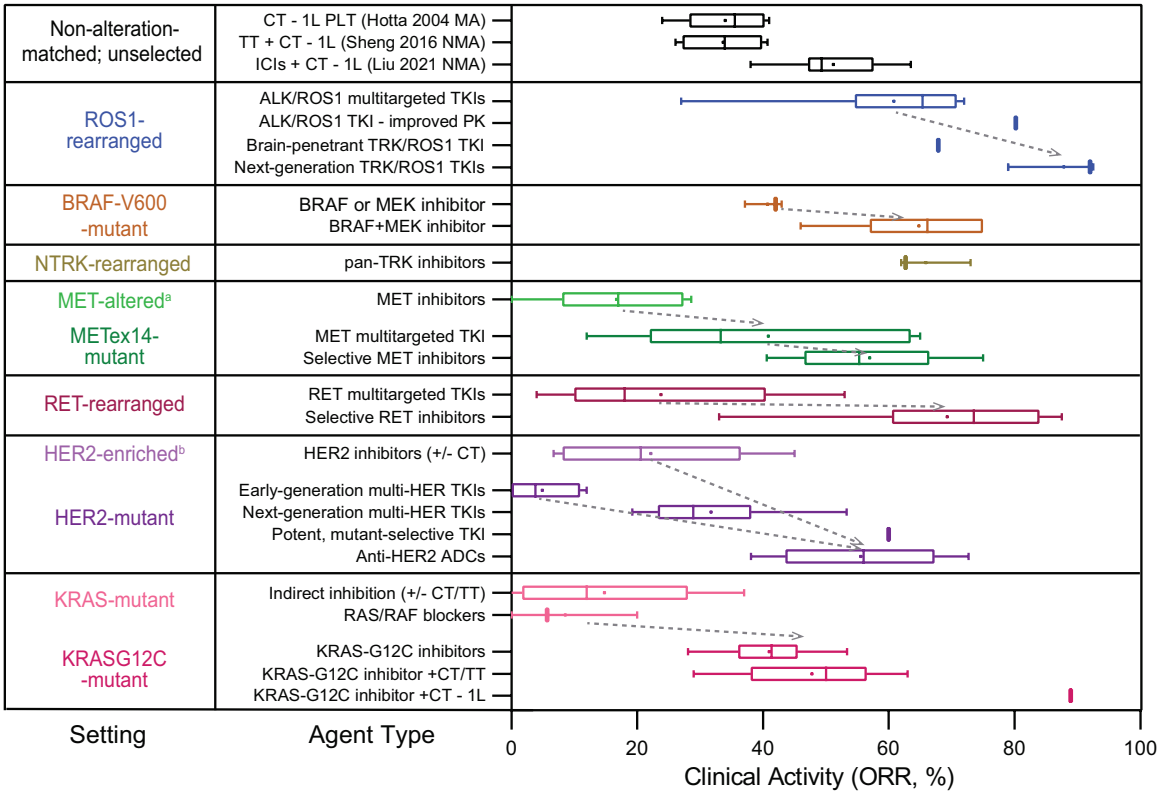

Figure 2. Clinical activity of selected types of agents used as initial targeted therapy across different oncogene-driven NSCLC settings.

Box and whiskers plot of full (horizontal line segments) and interquartile ranges (boxes), median (vertical lines inside the boxes) and mean (dots) ORR values from clinical studies grouped by setting and type of systemic agent. ORRs for first-line CT alone (platinum doublets),[313] with TT,[314] or ICIs[315] were obtained from meta-analyses and are provided as reference points. Studies of initial TT in alteration-drug-matched settings often include patients previously treated with standards of care for advanced, biomarker-unselected NSCLC. Studies in patients previously treated with alteration-matched TT were not included (e.g., studies of ROS1 inhibitors in patients previously treated with a ROS1 TKI).

[a]"Altered" was used to convey any alteration type, including amplification, overexpression, and mutation. Most of the alterations in "MET-altered" are in *MET*-amplified or -overexpressed but may also include a small fraction of patients with *MET* mutations.

[b]"Enriched" was used to convey increased levels of gene products (RNA or protein amplification or overexpression).

ADC, antibody–drug conjugate; ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma viral oncogene homolog; MA, meta-analysis; MEK, mitogen-activated protein kinase kinase; MET, hepatocyte growth factor receptor gene; NMA, network meta-analysis; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; PK, pharmacokinetics; PLT, platinum (doublets); RET, rearranged during transfection; ROS1, c-ros oncogene 1; RNA, ribonucleic acid; TKI, tyrosine kinase inhibitor; TRK, tropomyosin receptor kinase; TT, targeted therapy; 1L, first-line.

Our review highlights the considerable development of targeted therapy in NSCLC, resulting in an overall increase in the antitumor activity of alteration-drug-matched strategies across multiple oncogene-driven settings (Figure 2). Fueled by developments in molecular diagnostic tools, patient selection has evolved from biomarker-unselected populations to those defined by an altered biomarker and, more recently, by specific alterations with known oncogenic potential. Target actionability has also improved through the development of increasingly selective and potent agents, with better pharmacokinetic profiles, that are capable of inhibiting specific alterations at lower doses and with fewer off-target effects. Although the initial use of multi-targeted TKIs allowed multiple alterations to become simultaneously actionable (e.g., crizotinib in *ALK*-, *ROS1*-, and *MET*-altered disease), these agents have generally been replaced with more potent, selective, and/or direct small-molecule inhibitors or antibody-based agents. For example, even though crizotinib had initially shown considerable activity in ROS1-rearranged NSCLC, ORRs in this setting continue to improve with next-generation inhibitors that

display higher selectivity toward ROS1 and its mutant forms (Figure 2).[57–59,309] Nonetheless, strategies involving simultaneous inhibition of multiple targets such as co- and pan-inhibitory approaches may still be useful in areas where a more stringent biological control is required due to compensatory mechanisms (such as functional redundancy and pathway feedback loops) or weak primary target inhibition. With the establishment of alteration-drug-matched approaches as first-line therapy in the advanced setting, there is an increasing need for strategies to overcome both innate and acquired resistance.[310] These commonly involve co-inhibition with combination therapy or bispecific agents to address off-target mechanisms (e.g., KRAS-G12C plus SHP2 inhibitors against adaptative resistance to KRAS inhibition[123,124,310] or amivantamab to overcome reciprocal resistance and signaling crosstalk between EGFR and MET)[310–312] and/or use of next-generation inhibitors which typically address on-target resistance mechanisms (e.g., taletrectinib against the ROS1 secondary solvent-front mutation G2032R).[309] Current research also increasingly favors direct alteration targeting over indirect strategies such as modulation of proximal "pathway" components or levels of effector molecules or by stabilizing inactive/OFF states. Newer antibody-based agents are improving the clinical actionability of alteration-matched approaches by directed delivery of cytotoxic moieties (ADCs) or by specifically and simultaneously targeting multiple alterations with potential synergistic effects (bispecific antibodies). Bispecific antibodies have also the potential of combining alteration-drug-matching with other therapeutic approaches that have been successful in the treatment of NSCLC, such as immune modulation of the tumor microenvironment with ICIs.

Development of effective therapeutic strategies has been challenging in some biomarker-selected settings, such as *PI3K*- and *FGFR*-altered NSCLC for which no agent was approved despite decades-long research efforts. In particular, alterations to PI3K and its efferent (PI3K-AKT-mammalian target of rapamycin (mTOR)) pathway are relatively common in NSCLC and multiple direct and indirect inhibitory approaches have been attempted with pan-class I PI3K, PI3K subtype, AKT, mTOR, and PI3K/mTOR inhibitors in both alteration-drug-matched and -unmatched populations.[316–318] PI3K-AKT-mTOR is an example of a pathway with complex regulatory mechanisms and intricate crosstalk, where target inhibition is challenged by multiple intra- and inter-pathway compensatory mechanisms (including functional redundancy of PI3K isoforms) and on-target toxicities.[316–320] Moreover, PI3K pathway alterations are genetically diverse, occur in a clinically heterogenous group of patients, and are often associated with alterations in other oncogenes and high mutational load, where they may be "passengers" rather than "drivers" of the oncogenic process.[320–322] In addition to addressing issues with inhibitor selectivity and toxicity, and similar to MET inhibitors in *MET*-altered disease, a critical step in the development of PI3K inhibitors in NSCLC may be the identification and targeting of oncogenic drivers among the range of PI3K pathway alterations.[320]

It is important to note that many targeted agents are currently being developed in unselected/non-matched populations, using indirect ("pathway") inhibition strategies and targeting non-oncogene tumor-associated alterations. For example, treatment of NFE2L2/KEAP1-altered NSCLC is being attempted indirectly with glutaminase[323] and mTOR inhibitors.[324,325] ADCs targeting the human trophoblast cell surface glycoprotein antigen 2 (TROP2; datopotamab deruxtecan, sacituzumab govitecan, and SKB264) have recently shown promise in NSCLC in combination with ICIs[326,327] or as single agents.[328–330] However, their development has been directed toward TROP2-unselected populations as biomarker analyses have failed to establish TROP2 expression as a predictor of clinical activity.[328,331] Development of ADCs against other tumor-associated markers especially in populations with high levels of target expression is a promising approach that is currently being explored.[332–334]

Summary

Research in alteration-drug matching continues to evolve at a rapid pace in NSCLC. The number of settings defined by oncogenic alterations has increased and alteration targeting has become increasingly specific and effective with the refinement of biomarker selection criteria and the use of newer, more selective, and potent agents. Future developments should focus on the continued application of these principles to new settings and the exploration of novel ways to target oncogene-driven NSCLC.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Barbara Melosky: Conceptualization; Data curation; Funding acquisition; Methodology; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Rosalyn A. Juergens: Conceptualization; Data curation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Shantanu Banerji: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.

Adrian Sacher: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.

Paul Wheatley-Price: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.

Stephanie Snow: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.

Ming-Sound Tsao: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.

Natasha B. Leighl: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.

Ilidio Martins: Data curation; Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Parneet Cheema: Conceptualization; Writing – original draft; Writing – review & editing.

Geoffrey Liu: Conceptualization; Writing – original draft; Writing – review & editing.

Quincy S. C. Chu: Conceptualization; Data curation; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Acknowledgements
We would like to thank Deanna McLeod and Akhil Padmanabhan from Kaleidoscope Strategic Inc. for their research and editorial support.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funding for this review was provided through unrestricted educational grants from Hoffmann-La Roche Canada, Novartis Canada, Pfizer Canada, AstraZeneca Canada Inc., Bayer Canada, Eli Lilly Canada Inc., Bristol Myers Squibb Canada, and Amgen Canada Inc. No discussion or viewing of review content was permitted with sponsors at any stage of review development.

Competing interests
B.M. has served in a consultancy or advisory role and received honoraria from Merck, Hoffmann-La Roche, Pfizer, Novartis, Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, Eli Lilly, Novartis, and AstraZeneca. R.A.J. has served in a consultancy or advisory role for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, EMD Serono, Merck, Novartis, Pfizer, Hoffmann-La Roche, Sanofi, and Takeda, has received honoraria from AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, EMD Serono, Fusion Pharmaceuticals, Merck, Novartis, Pfizer, Hoffmann-La Roche, Sanofi, and Takeda, and has received research funding from AstraZeneca, Bristol-Myers Squibb, and Merck. S.B. has served in a consultancy or advisory role for AstraZeneca, Bayer, Janssen, Jazz, Bristol-Myers Squibb, and Hoffmann-La Roche, has immediate family members who have served in a consultancy or advisory role for Abbvie, AstraZeneca, Beigene, Janssen, Merck, and Eli Lilly, and has received research funding from AstraZeneca, Hoffmann-La Roche, and Jazz, and has immediate family members who have received research funding from AstraZeneca and Eli Lilly. A.S. has received honoraria from Amgen and Merck and has received research funding from AstraZeneca, Amgen, Genentech, Merck, Lilly, Pfizer, BMS, Spectrum, GSK, Iovance, CRISPR Therapeutics, BridgeBio, HotSpot Therapeutics, and AdaptImmune. P.W.-P. has served in a consultancy or advisory role for Takeda, Hoffmann-La Roche, Prizer, Bristol-Myers Squibb, Merck, AstraZeneca, Novartis, and Janssen, has received honoraria from Bayer, Merck, and AstraZeneca, and has received research funding from Turning Point, Hoffmann-La Roche, Merck, and AstraZeneca. S.S. has served in a consultancy or advisory role for Amgen, Astellas, Astra Zeneca, Bayer,

Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Knight Therapeutics, Elli Lilly, Merck, Novartis, Pfizer, Hoffmann-La Roche, Sanofi, Taiho, and Takeda, has received honoraria from Amgen, AstraZeneca, Bristol-Myers Squibb, Knight Therapeutics, Merck, Pfizer, Sanofi, Taiho, and Takeda, and has received research funding from Merck, Bristol-Myers Squibb, Sanofi, Novartis, Amgen, and AstraZeneca. M.-S.T. has served in a consultancy or advisory role for AstraZeneca, Amgen, Abbvie, Bayer, Sanofi, Regeneron, and Daiichi Sankyo, has received honoraria as speakers from Abbvie and Sanofi, and has received research funding from Bayer, AstraZeneca, and Sanofi. N.B.L. has received research funding from Pfizer, Roche, BMS, Array, Guardant Health, Amgen, Lilly, Takeda, MSD, and Bayer, and has received travel funding for CME lectures from AstraZeneca, MSD, Guardant, Sanofi, Hoffmann-La Roche, and Pfizer. I.M. has no conflicts of interest to disclose. P.C. has served in a consultancy or advisory role for Amgen, AstraZeneca, BMS, Hoffmann-La Roche, Janssen, Novartis, Merck, and Pfizer, has received honoraria from Merck, AstraZeneca, Sanofi, Eli Lilly, GSK, and Janssen, and has received other remuneration from Pfizer. G.L. has served in a consultancy or advisory role for Novartis, Jazz, Abbvie, Pfizer, Bristol-Myers Squibb, Amgen, AstraZeneca, Bayer, Takeda, Janssen, Merck, Boehringer Ingelheim, EMD Serono, and Hoffmann-La Roche, and has received research funding from Takeda, AstraZeneca, Bayer, EMD Serono, Amgen. Q.S.C.C. has served in a consultancy or advisory role for Abbvie, Amgen, AnHeart, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Eisai, Janssen, Jazz, Merck, Novartis, Ocellaris, Pfizer, Hoffmann-La Roche, and Takeda, has received honoraria from Abbvie, Amgen, AnHeart, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Eisai, Janssen, Jazz, Merck, Novartis, Ocellaris, Pfizer, Hoffmann-La Roche, and Takeda, and has received research funding from AstraZeneca.

Availability of data and materials

Not applicable.

ORCID iDs

Barbara Melosky https://orcid.org/0000-0003-2865-659X

Ming-Sound Tsao https://orcid.org/0000-0002-9160-5405

Quincy S. C. Chu https://orcid.org/0000-0003-4814-3126

Supplemental material

Supplemental material for this article is available online.

References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. *CA: Cancer J Clin* 2023; 73: 17–48.
2. Malvezzi M, Santucci C, Boffetta P, et al. European cancer mortality predictions for the year 2023 with focus on lung cancer. *Ann Oncol* 2023; 34: 410–419.
3. International Agency for Research on Cancer. Global Cancer Observatory, https://gco.iarc.fr/en (2024, accessed February 7, 2024).
4. Thai AA, Solomon BJ, Sequist LV, et al. Lung cancer. *Lancet* 2021; 398: 535–554.
5. Alduais Y, Zhang H, Fan F, et al. Non-small cell lung cancer (NSCLC): a review of risk factors, diagnosis, and treatment. *Medicine* 2023; 102: e32899.
6. American Cancer Society. Lung cancer—non-small cell: statistics, https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics (2023, accessed 7 February 2024).
7. Chu QS. Targeting non-small cell lung cancer: driver mutation beyond epidermal growth factor mutation and anaplastic lymphoma kinase fusion. *Ther Adv Med Oncol* 2020; 12: 1758835919895756.
8. Melosky B, Wheatley-Price P, Juergens RA, et al. The rapidly evolving landscape of novel targeted therapies in advanced non-small cell lung cancer. *Lung Cancer* 2021; 160: 136–151.
9. Tan AC and Tan DSW. Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. *J Clin Oncol* 2022; 40: 611–625.
10. Wang Z, Xing Y, Li B, et al. Molecular pathways, resistance mechanisms and targeted interventions in non-small-cell lung cancer. *Mol Biomed* 2022; 3: 42.
11. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung

cancer to gefitinib. *N Engl J Med* 2004; 350: 2129–2139.

12. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer. *Nature* 2007; 448: 561–566.
13. Kazandjian D, Blumenthal GM, Chen HY, et al. FDA approval summary: crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. *Oncologist* 2014; 19: e5–e11.
14. Cohen MH, Williams GA, Sridhara R, et al. FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets. *Oncologist* 2003; 8: 303–336.
15. Riedl JM, Moik F, Esterl T, et al. Molecular diagnostics tailoring personalized cancer therapy-an oncologist's view. *Virchows Arch* 2024; 484: 169–179.
16. Sethi S, Ali S, Philip PA, et al. Clinical advances in molecular biomarkers for cancer diagnosis and therapy. *Int J Mol Sci* 2013; 14: 14771–14784.
17. Steeghs EMP, Groen HJM, Schuuring E, et al. Mutation-tailored treatment selection in non-small cell lung cancer patients in daily clinical practice. *Lung Cancer* 2022; 167: 87–97.
18. Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov* 2017; 7: 596–609.
19. Stephan-Falkenau S, Streubel A, Mairinger T, et al. Landscape of genomic alterations and PD-L1 expression in early-stage non-small-cell lung cancer (NSCLC)—a single center, retrospective observational study. *Int J Mol Sci* 2022; 23: 12511.
20. Friedlaender A, Perol M, Banna GL, et al. Oncogenic alterations in advanced NSCLC: a molecular super-highway. *Biomark Res* 2024; 12: 24.
21. Jalal SI, Guo A, Ahmed S, et al. Analysis of actionable genetic alterations in lung carcinoma from the VA National Precision Oncology Program. *Semin Oncol* 2022; 49: 265–274.
22. Fois SS, Paliogiannis P, Zinellu A, et al. Molecular epidemiology of the main druggable genetic alterations in non-small cell lung cancer. *Int J Mol Sci* 2021; 22: 612.
23. Li J, Chen S, Xue H, et al. Genomic alteration spectrum of non-small cell lung cancer patients in East-China characterized by tumor tissue DNA and cell-free DNA. *Onco Targets Ther* 2022; 15: 571–584.
24. Stencel K, Chmielewska I, Milanowski J, et al. Non-small-cell lung cancer: new rare targets-new targeted therapies-state of the art and future directions. *Cancers* 2021; 13: 1829.
25. Barlesi F, Mazieres J, Merlio JP, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). *Lancet* 2016; 387: 1415–1426.
26. La Fleur L, Falk-Sörqvist E, Smeds P, et al. Mutation patterns in a population-based non-small cell lung cancer cohort and prognostic impact of concomitant mutations in KRAS and TP53 or STK11. *Lung Cancer* 2019; 130: 50–58.
27. Sehgal K, Patell R, Rangachari D, et al. Targeting ROS1 rearrangements in non-small cell lung cancer with crizotinib and other kinase inhibitors. *Transl Cancer Res* 2018; 7: S779–S786.
28. Ou SI, Zhu VW and Nagasaka M. Catalog of 5' fusion partners in ALK-positive NSCLC circa 2020. *JTO Clin Res Rep* 2020; 1: 100015.
29. Yang X, Tang Z, Li J, et al. Progress of non-small-cell lung cancer with ROS1 rearrangement. *Front Mol Biosci* 2023; 10.
30. O'Leary CG, Andelkovic V, Ladwa R, et al. Targeting BRAF mutations in non-small cell lung cancer. *Transl Lung Cancer Res* 2019; 8: 1119–1124.
31. Solomon JP and Hechtman JF. Detection of NTRK fusions: merits and limitations of current diagnostic platforms. *Cancer Res* 2019; 79: 3163–3168.
32. Farago AF, Taylor MS, Doebele RC, et al. Clinicopathologic features of non-small-cell lung cancer harboring an NTRK gene fusion. *JCO Precis Oncol* 2018; 2018: PO.18.00037.
33. Liu F, Wei Y, Zhang H, et al. NTRK fusion in non-small cell lung cancer: diagnosis, therapy, and TRK inhibitor resistance. *Front Oncol* 2022; 12: 864666.
34. Forsythe A, Zhang W, Phillip Strauss U, et al. A systematic review and meta-analysis of neurotrophic tyrosine receptor kinase gene fusion frequencies in solid tumors. *Ther Adv Med Oncol* 2020; 12: 1758835920975613.
35. Liang H and Wang M. MET oncogene in non-small cell lung cancer: mechanism of MET dysregulation and agents targeting the HGF/c-Met axis. *Onco Targets Ther* 2020; 13: 2491.
36. Bronte G, Ulivi P, Verlicchi A, et al. Targeting RET-rearranged non-small-cell lung cancer: future prospects. *Lung Cancer* 2019; 10: 27–36.

37. Drilon A, Hu ZI, Lai GGY, et al. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. *Nat Rev Clin Oncol* 2018; 15: 151–167.

38. Zhao J and Xia Y. Targeting HER2 alterations in non-small-cell lung cancer: a comprehensive review. *JCO Precis Oncol* 2020; 4: 411–425.

39. Ren S, Wang J, Ying J, et al. Consensus for HER2 alterations testing in non-small-cell lung cancer. *ESMO Open* 2022; 7: 100395.

40. Riudavets M, Sullivan I, Abdayem P, et al. Targeting HER2 in non-small-cell lung cancer (NSCLC): a glimpse of hope? An updated review on therapeutic strategies in NSCLC harbouring HER2 alterations. *ESMO Open* 2021; 6: 100260.

41. Martin P, Leighl NB, Tsao M-S, et al. KRAS mutations as prognostic and predictive markers in non–small cell lung cancer. *J Thorac Oncol* 2013; 8: 530–542.

42. Knickelbein K and Zhang L. Mutant KRAS as a critical determinant of the therapeutic response of colorectal cancer. *Genes Dis* 2015; 2: 4–12.

43. Cascetta P, Marinello A, Lazzari C, et al. KRAS in NSCLC: state of the art and future perspectives. *Cancers* 2022; 14(21): 5430.

44. Xie M, Xu X and Fan Y. KRAS-mutant non-small cell lung cancer: an emerging promisingly treatable subgroup. *Front Oncol* 2021; 11: 672612.

45. Michels SYF, Franklin J, Massuti B, et al. Crizotinib in ROS1-rearranged lung cancer (EUCROSS): updated overall survival. *J Clin Oncol* 2022; 40 (Suppl. 16): 9078.

46. Michels S, Massutí B, Schildhaus H-U, et al. 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* 2019; 14: 1266–1276.

47. Michels S, Massutí B, Vasyliv I, et al. Overall survival and central nervous system activity of crizotinib in ROS1-rearranged lung cancer-final results of the EUCROSS trial. *ESMO Open* 2024; 9: 102237.

48. Landi L, Chiari R, Tiseo M, et al. Crizotinib in MET-deregulated or ROS1-rearranged pretreated non-small cell lung cancer (METROS): a phase II, prospective, multicenter, two-arms trial. *Clin Cancer Res* 2019; 25: 7312–7319.

49. Cappuzzo F, Chiari R, Tiseo M, et al. EP08.02-048 crizotinib in ROS1+NSCLC: long-term OS analysis in patients with brain metastases included in the phase II METROS Trial. *J Thorac Oncol* 2022; 17(Suppl. 9): S421 [conference abstract].

50. Wu YL, Lu S, Yang JC, et al. Final overall survival, safety, and quality of life results from a phase 2 study of crizotinib in East Asian patients with ROS1-positive advanced NSCLC. *JTO Clin Res Rep* 2022; 3: 100406.

51. Wu Y-L, Yang JC-H, Kim D-W, et al. Phase II study of crizotinib in East Asian patients with ROS1-positive advanced non-small-cell lung cancer. *J Clin Oncol* 2018; 36: 1405–1411.

52. Drilon A, Chiu CH, Fan Y, et al. Long-term efficacy and safety of entrectinib in ROS1 fusion-positive NSCLC. *JTO Clin Res Rep* 2022; 3: 100332.

53. Lu S, Pan H, Wu L, et al. Efficacy, safety and pharmacokinetics of Unecritinib (TQ-B3101) for patients with ROS1 positive advanced non-small cell lung cancer: a Phase I/II Trial. *Signal Transduct Target Ther* 2023; 8: 249.

54. Toyozawa R, Niho S, Goto Y, et al. 977P Phase II study of brigatinib in patients with tyrosine kinase inhibitor (TKI)- naïve ROS1-rearranged advanced non-small cell lung cancer (NSCLC): Barossa cohort 1. *Ann Oncol* 2022; 33: S996–S997.

55. Ai X, Wang Q, Cheng Y, et al. Safety but limited efficacy of ensartinib in ROS1-positive NSCLC: a single-arm, multicenter phase 2 study. *J Thorac Oncol* 2021; 16: 1959–1963.

56. Drilon A, Camidge DR, Lin JJ, et al. Repotrectinib in ROS1 fusion-positive non-small-cell lung cancer. *N Engl J Med* 2024; 390: 118–131.

57. Li W, Yang N, Li K, et al. 14MO Updated efficacy and safety of taletrectinib in patients (pts) with ROS1+ non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2023; 18 (Suppl. 4): S47–S48.

58. Pérol M, Yang N, Choi CM, et al. 1373P Efficacy and safety of taletrectinib in patients (Pts) with ROS1+ non-small cell lung cancer (NSCLC): interim analysis of global TRUST-II study. *Ann Oncol* 2023; 34: S788–S789.

59. Drilon A, Besse B, Camidge DR, et al. Safety and preliminary clinical activity of NVL-520, a highly selective ROS1 inhibitor, in patients with advanced ROS1 fusion-positive solid tumors. *Eur J Cancer* 2022; 174: S6–S7

60. Planchard D, Besse B, Groen HJM, et al. Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-year survival rates and genomic analysis. *J Thorac Oncol* 2022; 17: 103–115.

61. Planchard D, Besse B, Groen HJM, et al. 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* 2016; 17: 984–993.

62. Planchard D, Smit EF, Groen HJM, et al. 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* 2017; 18: 1307–1316.
63. Fan Y, Jianying Z, Yuanyuan Z, et al. EP08.02-052 Safety and efficacy of dabrafenib plus trametinib in Chinese patients with BRAF V600E- mutation positive metastatic NSCLC. *J Thorac Oncol* 2022; 17(Suppl. 9): S423.
64. Riely GJ, Smit EF, Ahn MJ, et al. Phase II, open-label study of encorafenib plus binimetinib in patients with BRAF(V600)-mutant metastatic non-small-cell lung cancer. *J Clin Oncol* 2023; 41: 3700–3711.
65. Shi Y, Zheng Y, Chen J, et al. 1378P Efficacy and safety of tunlametinib (HL-085) combined with vemurafenib in patients with advanced BRAF V600-mutated solid tumors: a multicenter, phase I study. *Ann Oncol* 2023; 34: S790.
66. Drilon A, Tan DSW, Lassen UN, et al. Efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase fusion-positive lung cancers. *JCO Precis Oncol* 2022; 6: e2100418.
67. Cho BC, Chiu CH, Massarelli E, et al. Updated efficacy and safety of entrectinib in NTRK fusion-positive non-small cell lung cancer. *Lung Cancer* 2024; 188: 107442.
68. Solomon B, Drilon A, Lin J, et al. 1372P Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: update from the phase I/II TRIDENT-1 trial. *Ann Oncol* 2023; 34: S787–S788.
69. Camidge DR, Otterson GA, Clark JW, et al. Crizotinib in patients with MET-amplified NSCLC. *J Thorac Oncol* 2021; 16: 1017–1029.
70. Wolf J, Seto T, Han JY, et al. Capmatinib in MET Exon 14-Mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med* 2020; 383: 944–957.
71. Le X, Paz-Ares LG, Meerbeeck JV, et al. Tepotinib in patients (pts) with advanced non-small cell lung cancer (NSCLC) with MET amplification (METamp). *J Clin Oncol* 2021; 39(Suppl. 15): 9021.
72. Dagogo-Jack I, Moonsamy P, Gainor JF, et al. A phase 2 study of capmatinib in patients with MET-altered lung cancer previously treated with a MET inhibitor. *J Thorac Oncol* 2021; 16: 850–859.
73. Kollmannsberger C, Hurwitz H, Bazhenova L, et al. Phase I study evaluating glesatinib (MGCD265), an inhibitor of MET and AXL, in patients with non-small cell lung cancer and other advanced solid tumors. *Target Oncol* 2023; 18: 105–118.
74. Hu X, Cui X, Wang Z, et al. Safety, efficacy and pharmacokinetics of BPI-9016M in c-MET overexpression or MET exon 14 skipping mutation patients with locally advanced or metastatic non-small-cell lung cancer: a phase Ib study. *BMC Cancer* 2023; 23: 331.
75. Cho BC, Ahn M, Kim T, et al. 1173P Early safety, tolerability, and efficacy of REGN5093 in patients (pts) with MET-altered advanced non-small cell lung cancer (aNSCLC) from a first in human (FIH) study. *Ann Oncol* 2022; 33: S1085.
76. Camidge DR, Bar J, Horinouchi H, et al. Telisotuzumab vedotin (Teliso-V) monotherapy in patients (pts) with previously treated c-Met–overexpressing (OE) advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2022; 40(Suppl. 16): 9016.
77. Waqar SN, Redman MW, Arnold SM, et al. A phase II study of telisotuzumab vedotin in patients with c-MET-positive stage IV or recurrent squamous cell lung cancer (LUNG-MAP sub-study S1400K, NCT03574753). *Clin Lung Cancer* 2021; 22: 170–177.
78. Wolf J, Garon EB, Groen HJM, et al. Capmatinib in MET exon 14-mutated, advanced NSCLC: updated results from the GEOMETRY mono-1 study. *J Clin Oncol* 2021; 39(Suppl. 15): 9020.
79. Vidal OJ, Singhal M, Alvarez R, et al. 1391P Capmatinib vs docetaxel as second-or third-line (2/3L) therapy in patients (pts) with METex14-mutated advanced NSCLC (aNSCLC): the GeoMETry-III trial. *Ann Oncol* 2023; 34: S797.
80. Mazieres J, Paik PK, Garassino MC, et al. Tepotinib treatment in patients with MET exon 14-skipping non-small cell lung cancer: long-term follow-up of the VISION phase 2 nonrandomized clinical trial. *JAMA Oncol* 2023; 9: 1260–1266.
81. Paik PK, Felip E, Veillon R, et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. *N Engl J Med* 2020; 383: 931–943.
82. Yu Y, Zhou J, Li X, et al. Gumarontinib in patients with non-small-cell lung cancer harbouring MET exon 14 skipping mutations: a multicentre, single-arm, open-label, phase 1b/2 trial. *EClinicalMedicine* 2023; 59: 101952.

83. Yang J-J, Zhang Y, Wu L, et al. 1379P Preliminary results of phase II KUNPENG study of vebreltinib in patients (Pts) with advanced NSCLC harboring c-MET alterations. *Ann Oncol* 2023; 34: S791.

84. Lu S, Fang J, Li X, et al. Long-term efficacy, safety, and subgroup analysis of savolitinib in Chinese patients with NSCLCs harboring MET exon 14 skipping alterations. *JTO Clin Res Rep* 2022; 3: 100407.

85. Lu S, Fang J, Li X, et al. Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring MET exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study. *Lancet Respir Med* 2021; 9: 1154–1164.

86. Krebs M, Spira AI, Cho BC, et al. Amivantamab in patients with NSCLC with MET exon 14 skipping mutation: updated results from the CHRYSALIS study. *J Clin Oncol* 2022; 40(Suppl. 16): 9008.

87. Takeuchi S, Yanagitani N, Seto T, et al. Phase 1/2 study of alectinib in RET-rearranged previously-treated non-small cell lung cancer (ALL-RET). *Transl Lung Cancer Res* 2021; 10: 314–325.

88. Drilon A, Subbiah V, Gautschi O, et al. Selpercatinib in patients with ret fusion-positive non-small-cell lung cancer: updated safety and efficacy from the registrational LIBRETTO-001 phase I/II trial. *J Clin Oncol* 2023; 41: 385–394.

89. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. *N Engl J Med* 2020; 383: 813–824.

90. Lu S, Cheng Y, Huang D, et al. Efficacy and safety of selpercatinib in Chinese patients with advanced RET fusion-positive non-small-cell lung cancer: a phase II clinical trial (LIBRETTO-321). *Ther Adv Med Oncol* 2022; 14: 17588359221105020.

91. Zhou C, Solomon B, Loong HH, et al. First-line selpercatinib or chemotherapy and pembrolizumab in RET fusion-positive NSCLC. *N Engl J Med* 2023; 389: 1839–1850.

92. Griesinger F, Curigliano G, Thomas M, et al. Safety and efficacy of pralsetinib in RET fusion-positive non-small-cell lung cancer including as first-line therapy: update from the ARROW trial. *Ann Oncol* 2022; 33: 1168–1178.

93. Schoffski P, Cho BC, Italiano A, et al. BOS172738, a highly potent and selective RET inhibitor, for the treatment of RET-altered tumors including RET-fusion+ NSCLC and RET-mutant MTC: phase 1 study results. *J Clin Oncol* 2021; 39(Suppl. 15): 3008.

94. Zhou Q, Wu Y-L, Zheng X, et al. A phase I study of KL590586, a next-generation selective RET inhibitor, in patients with RET-altered solid tumors. *J Clin Oncol* 2023; 41(Suppl. 16): 3007.

95. Zhou C, Li W, Zhang Y, et al. A first-in-human phase I, dose-escalation and dose-expansion study of SY-5007, a highly potent and selective RET inhibitor, in Chinese patients with advanced RET positive solid tumors. *J Clin Oncol* 2023; 41(Suppl. 16): 9111.

96. Elamin YY, Robichaux JP, Carter BW, et al. Poziotinib for patients with HER2 exon 20 mutant non-small-cell lung cancer: results from a phase II trial. *J Clin Oncol* 2022; 40: 702–709.

97. Socinski M, Cornelissen R, Garassino M, et al. LBA60 ZENITH20, a multinational, multi-cohort phase II study of poziotinib in NSCLC patients with EGFR or HER2 exon 20 insertion mutations. *Ann Oncol* 2020; 31: S1188.

98. Cornelissen R, Prelaj A, Sun S, et al. Poziotinib in treatment-naïve NSCLC harboring HER2 exon 20 mutations: ZENITH20-4, a multicenter, multicohort, open-label, phase 2 trial (cohort 4). *J Thorac Oncol* 2023; 18: 1031–1041.

99. Le X, Cornelissen R, Garassino M, et al. Poziotinib in non-small-cell lung cancer harboring HER2 exon 20 insertion mutations after prior therapies: ZENITH20-2 trial. *J Clin Oncol* 2022; 40: 710–718.

100. Song Z, Li Y, Chen S, et al. Efficacy and safety of pyrotinib in advanced lung adenocarcinoma with HER2 mutations: a multicenter, single-arm, phase II trial. *BMC Med* 2022; 20: 42.

101. Liu SM, Tu HY, Wei XW, et al. First-line pyrotinib in advanced HER2-mutant non-small-cell lung cancer: a patient-centric phase 2 trial. *Nat Med* 2023; 29: 2079-86.

102. Yang G, Xu H, Yang Y, et al. Pyrotinib combined with apatinib for targeting metastatic non-small cell lung cancer with HER2 alterations: a prospective, open-label, single-arm phase 2 study (PATHER2). *BMC Med* 2022; 20: 277.

103. Loong H, Daniele G, Yang T, et al. 1320MO Early evidence of efficacy in patients (pts) with non-small cell lung cancer (NSCLC) with HER2 exon20 insertion (ex20ins) mutations treated in a phase I study with BAY 2927088. *Ann Oncol* 2023; 34: S761–S762.

104. Opdam F, Heymach J, Ruiter G, et al. 1375P Beamion Lung 1, an ongoing phase Ia/Ib trial of the HER2 TKI, BI 1810631 in patients

(pts) with advanced solid tumors with HER2 aberrations: latest data. *Ann Oncol* 2023; 34: S789–S790.

105. Heymach J, Opdam F, Barve MA, et al. Phase I Beamion Lung 1 trial of BI 1810631, a HER2 tyrosine kinase inhibitor (TKI), as monotherapy in patients (pts) with advanced/metastatic solid tumors with HER2 aberrations: updated data. *J Clin Oncol* 2023; 41(Suppl. 16): 8545.
106. Fang W, Zhao Y, Huang Y, et al. Safety and efficacy of inetetamab in combination with pyrotinib in HER2 mutant patients with non-small cell lung cancer (NSCLC): an open-label, phase Ib trial. *J Clin Oncol* 2023; 41(Suppl. 16): 9105.
107. Ganti AK, Rothe M, Mangat PK, et al. Pertuzumab plus trastuzumab in patients with lung cancer with ERBB2 mutation or amplification: results from the targeted agent and profiling utilization registry study. *JCO Precis Oncol* 2023; 7: e2300041.
108. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted therapy for advanced solid tumors on the basis of molecular profiles: results from MyPathway, an Open-Label, Phase IIa Multiple Basket Study. *J Clin Oncol* 2018; 36: 536–542.
109. Mazieres J, Lafitte C, Ricordel C, et al. Combination of trastuzumab, pertuzumab, and docetaxel in patients with advanced non–small-cell lung cancer harboring HER2 mutations: results from the IFCT-1703 R2D2 trial. *J Clin Oncol* 2022; 40: 719–728.
110. Iwama E, Zenke Y, Sugawara S, et al. Trastuzumab emtansine for patients with non-small cell lung cancer positive for human epidermal growth factor receptor 2 exon-20 insertion mutations. *Eur J Cancer* 2022; 162: 99–106.
111. Jebbink M, de Langen AJ, Monkhorst K, et al. Trastuzumab-emtansine and osimertinib combination therapy to target HER2 bypass track resistance in EGFR mutation-positive NSCLC. *JTO Clin Res Rep* 2023; 4: 100481.
112. Smit EF, Felip E, Uprety D, et al. Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial. *Lancet Oncol* 2024; 25: 439–454.
113. Li BT, Smit EF, Goto Y, et al. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. *N Engl J Med* 2022; 386: 241–251.
114. Smit EF, Nakagawa K, Nagasaka M, et al. 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* 2020; 38(Suppl. 15): 9504.
115. Goto K, Goto Y, Kubo T, et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small-cell lung cancer: primary results from the randomized, phase II destiny-lung02 trial. *J Clin Oncol* 2023; 41: 4852–4863.
116. Dy GK, Govindan R, Velcheti V, et al. Long-term outcomes and molecular correlates of sotorasib efficacy in patients with pretreated KRAS G12C-mutated non-small-cell lung cancer: 2-year analysis of CodeBreaK 100. *J Clin Oncol* 2023; 41: 3311–3317.
117. de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRAS(G12C) mutation: a randomised, open-label, phase 3 trial. *Lancet* 2023; 401: 733–746.
118. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a KRAS(G12C) mutation. *N Engl J Med* 2022; 387: 120–131.
119. Sacher A, LoRusso P, Patel MR, et al. Single-agent divarasib (GDC-6036) in solid tumors with a KRAS G12C mutation. *N Engl J Med* 2023; 389: 710–721.
120. Li Z, Song Z, Zhao Y, et al. D-1553 (Garsorasib), a potent and selective inhibitor of KRAS(G12C) in patients with NSCLC: phase 1 study results. *J Thorac Oncol* 2023; 18: 940–951.
121. Cassier PA, Dooms CA, Gazzah A, et al. KontRASt-01 update: safety and efficacy of JDQ443 in KRAS G12C-mutated solid tumors including non-small cell lung cancer (NSCLC). *J Clin Oncol* 2023; 41(Suppl. 16): 9007.
122. Li BT, Falchook GS, Durm GA, et al. OA03.06 CodeBreaK 100/101: first report of safety/efficacy of sotorasib in combination with pembrolizumab or atezolizumab in advanced KRAS p.G12C NSCLC. *J Thorac Oncol* 2022; 17(Suppl. 9): S10–S11.
123. Falchook G, Li BT, Marrone KA, et al. OA03.03 Sotorasib in combination with RMC-4630, a SHP2 inhibitor, in KRAS p.G12C-mutated NSCLC and other solid tumors. *J Thorac Oncol* 2022; 17(Suppl. 9): S8.
124. Wang J, Zhao J, Zhong J, et al. 653O Glecirasib (KRAS G12C inhibitor) in combination with JAB-3312 (SHP2 inhibitor) in patients with KRAS p.G12C mutated solid tumors. *Ann Oncol* 2023; 34: S459.

125. Reuss JE, Gandhi SG, Spigel DR, et al. RAMP 202: a phase 2 study of avutometinib (VS-6766) ± defactinib, in patients with advanced KRAS G12V mutant non–small cell lung cancer (NSCLC). *J Clin Oncol* 2023; 41(Suppl. 16): 9100.

126. Gadgeel SM, Miao J, Riess JW, et al. Phase II Study of Docetaxel and Trametinib in Patients with KRAS Mutation Positive Recurrent Non-Small Cell Lung Cancer (NSCLC; SWOG S1507, NCT-02642042). *Clin Cancer Res* 2023; 29: 3641–3649.

127. Garassino MC, Theelen WSME, Jotte R, et al. LBA65 KRYSTAL-7: efficacy and safety of adagrasib with pembrolizumab in patients with treatment-naïve, advanced non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation. *Ann Oncol* 2023; 34: S1309–S1310.

128. Sakata S, Akamatsu H, Azuma K, et al. The primary endpoint analysis of SCARLET study: a single-arm, phase II study of sotorasib plus carboplatin-pemetrexed in patients with advanced non-squamous, non-small cell lung cancer with KRAS G12C mutation (WJOG14821L). *J Clin Oncol* 2023; 41 (suppl. 16): 9006.

129. Arbour KC, Punekar S, Garrido-Laguna I, et al. 652O Preliminary clinical activity of RMC-6236, a first-in-class, RAS-selective, tri-complex RAS-MULTI(ON) inhibitor in patients with KRAS mutant pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC). *Ann Oncol* 2023; 34: S458.

130. Nogova L, Malchers F, Hillmer A, et al. 1329P FIND: a phase II study to evaluate the efficacy of erdafitinib in FGFR-altered NSCLC. *Ann Oncol* 2023; 34: S767.

131. Schram A, Goto K, Kim DW, et al. 1315MO Durable efficacy of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced NRG1 fusion-positive (NRG1+) non-small cell lung cancer (NSCLC). *Ann Oncol* 2023; 34: S756–S757.

132. Cho B, Johnson M, Bar J, et al. 655O Phase Ib study of cofetuzumab pelidotin, an anti-PTK7 antibody-drug conjugate, in patients with PTK7-expressing recurrent non-small cell lung cancer (rNSCLC). *Ann Oncol* 2023; 34: S460–S461.

133. Vilachã JF, Wassenaar TA and Marrink SJ. Structural aspects of the ROS1 kinase domain and oncogenic mutations. *Crystals* 2024; 14: 106.

134. Somwar R, Hofmann NE, Smith B, et al. NTRK kinase domain mutations in cancer variably impact sensitivity to type I and type II inhibitors. *Commun Biol* 2020; 3: 776.

135. Daga H, Niho S, Sakakibara-Konishi J, et al. Phase II study of brigatinib in ROS1 positive non-small cell lung cancer (NSCLC) patients previously treated with crizotinib: Barossa cohort 2. *J Clin Oncol* 2021; 39(Suppl. 15): 9040.

136. Ma Y, Zhao H, Xue J, et al. First-in-human phase I study of TQ-B3139 (CT-711) in advanced non-small cell lung cancer patients with ALK and ROS1 rearrangements. *Eur J Cancer* 2022; 173: 238–249.

137. Schneider JL, Muzikansky A, Lin JJ, et al. A phase 2 study of lorlatinib in patients with ROS1-rearranged lung cancer with brain-only progression on crizotinib. *JTO Clin Res Rep* 2022; 3: 100347.

138. Shi Y, Fang J, Hao X, et al. Safety and activity of WX-0593 (Iruplinalkib) in patients with ALK- or ROS1-rearranged advanced non-small cell lung cancer: a phase 1 dose-escalation and dose-expansion trial. *Signal Transduct Target Ther* 2022; 7: 25.

139. Zhao H, Chen J, Song Z, et al. First-in-human phase I results of APG-2449, a novel FAK and third-generation ALK/ ROS1 tyrosine kinase inhibitor (TKI), in patients (pts) with second-generation TKI-resistant ALK/ROS1+ non–small cell lung cancer (NSCLC) or mesothelioma. *J Clin Oncol* 2022; 40 (Suppl. 16): 9071.

140. Moro-Sibilot D, Cozic N, Pérol M, et al. Crizotinib in c-MET-or ROS1-positive NSCLC: results of the AcSé phase II trial. *Ann Oncol* 2019; 30: 1985–1991.

141. Shaw A, Riely G, Bang Y-J, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol* 2019; 30: 1121–1126.

142. Lim SM, Kim HR, Lee J-S, et al. Open-label, multicenter, phase II study of ceritinib in patients with non–small-cell lung cancer harboring ROS1 rearrangement. *J Clin Oncol* 2017; 35: 2613–2618.

143. Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial. *Lancet Oncol* 2019; 20: 1691–1701.

144. Cho B, Lin J, Camidge D, et al. Pivotal topline data from the phase 1/2 TRIDENT-1 trial of

repotrectinib in patients with ROS1+ advanced non-small cell lung cancer (NSCLC). *Eur J Cancer* 2022; 174: S1–S2.

145. Li W, Yang N, Ma H, et al. The efficacy and safety of taletrectinib in patients with TKI-naïve or crizotinib-pretreated ROS1-positive non–small cell lung cancer (NSCLC). *J Clin Oncol* 2022; 40 (Suppl. 16): 8572.

146. Papadopoulos KP, Borazanci E, Shaw AT, et al. U.S. Phase I first-in-human study of taletrectinib (DS-6051b/AB-106), a ROS1/TRK inhibitor, in patients with advanced solid tumors. *Clin Cancer Res* 2020; 26: 4785–4794.

147. Ou SI, Fujiwara Y, Shaw AT, et al. Efficacy of taletrectinib (AB-106/DS-6051b) in ROS1+ NSCLC: an updated pooled analysis of U.S. and Japan phase 1 studies. *JTO Clin Res Rep* 2021; 2: 100108.

148. U.S. Food and Drug Administration. *FDA approves crizotinib capsules*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-crizotinib-capsules (2016, accessed November 16, 2023).

149. U.S. Food and Drug Administration. *FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc (2019, accessed 16 November 2023).

150. Yun MR, Kim DH, Kim SY, et al. Repotrectinib exhibits potent antitumor activity in treatment-naïve and solvent-front-mutant ROS1-rearranged non-small cell lung cancer. *Clin Cancer Res* 2020; 26: 3287–3295.

151. BMS. Updated data from TRIDENT-1 trial show durable efficacy benefits with repotrectinib for patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer, https://news.bms.com/news/details/2023/Updated-Data-from-TRIDENT-1-Trial-Show-Durable-Efficacy-Benefits-with-Repotrectinib-for-Patients-with-Locally-Advanced-or-Metastatic-ROS1-Positive-Non-Small-Cell-Lung-Cancer/default.aspx (2023, accessed 16 November 2023).

152. U.S. Food and Drug Administration. *FDA approves repotrectinib for ROS1-positive non-small cell lung cancer*. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-repotrectinib-ros1-positive-non-small-cell-lung-cancer (2023, accessed 16 November 2023).

153. Fujiwara Y, Takeda M, Yamamoto N, et al. Safety and pharmacokinetics of DS-6051b in Japanese patients with non-small cell lung cancer harboring ROS1 fusions: a phase I study. *Oncotarget* 2018; 9: 23729–23737.

154. Sternberg A. FDA Grants breakthrough therapy designation to taletrectinib for ROS1+ non–small cell lung cancer, https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-designation-to-taletrectinib-for-ros1-non-small-cell-lung-cancer (2023, accessed November 16, 2023).

155. Sakakibara-Konishi J, Niho S, Daga H, et al. P45.04 phase II study of brigatinib in ROS1 positive non-small cell lung cancer (NSCLC) patients previously treated with crizotinib: Barossa Cohort 2. *J Thorac Oncol* 2021; 16: S1086.

156. Johnson TW, Richardson PF, Bailey S, et al. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. *J Med Chem* 2014; 57: 4720–4744.

157. Wolf J, Planchard D, Heist RS, et al. 1387P Phase Ib study of LXH254+ LTT462 in patients with KRAS-or BRAF-mutant NSCLC. *Ann Oncol* 2020; 31: S881–S882.

158. Subbiah V, Gervais R, Riely G, et al. 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* 2019; 3: PO.18.00266.

159. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med* 2015; 373: 726–736.

160. Subbiah V, Sen S, Hess KR, et al. 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* 2018; 2: PO.18.00189.

161. Kim TW, Lee J, Kim TM, et al. 529P A phase Ib trial of belvarafenib in combination with cobimetinib in patients (pts) with RAS- or RAF- mutated (m) solid tumors: updated safety data and indication-specific efficacy results. *Ann Oncol* 2021; 32: S595.

162. Lopez-Chavez A, Thomas A, Rajan A, et al. Molecular profiling and targeted therapy for

advanced thoracic malignancies: a biomarker-derived, multiarm, multihistology phase II basket trial. *J Clin Oncol* 2015; 33: 1000–1007.

163. U.S. Food and Drug Administration. *FDA grants regular approval to dabrafenib and trametinib combination for metastatic NSCLC with BRAF V600E mutation*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-dabrafenib-and-trametinib-combination-metastatic-nsclc-braf-v600e (2017, accessed 30 November 2023).

164. Liu Y, Cheng Y, Huang G, et al. Preclinical characterization of tunlametinib, a novel, potent, and selective MEK inhibitor. *Front Pharmacol* 2023; 14: 1271268.

165. Sforza V, Palumbo G, Cascetta P, et al. BRAF inhibitors in non-small cell lung cancer. *Cancers* 2022; 14: 4863.

166. U.S. Food and Drug Administration. *FDA approves encorafenib with binimetinib for metastatic non-small cell lung cancer with a BRAF V600E mutation*. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-binimetinib-metastatic-non-small-cell-lung-cancer-braf-v600e-mutation (2023, accessed 30 November 2023).

167. Schram AM, Subbiah V, Sullivan R, et al. Abstract CT031: a first-in-human, phase 1a/1b, open-label, dose-escalation and expansion study to investigate the safety, pharmacokinetics, and antitumor activity of the RAF dimer inhibitor BGB-3245 in patients with advanced or refractory tumors. *Cancer Res* 2023; 83(Suppl. 8): CT031.

168. Bulfer SL, Bourdonnec BL, Zwicker JD, et al. Abstract 4045: DCC-3084, a RAF dimer inhibitor, broadly inhibits BRAF class I, II, III, BRAF fusions, and RAS-driven solid tumors leading to tumor regression in preclinical models. *Cancer Res* 2023; 83 (Suppl. 7): 4045.

169. Beck JTT, McKean M, Gadgeel SM, et al. A phase 1, open-label, dose escalation and dose expansion study to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of PF-07799933 (ARRY-440) as a single agent and in combination therapy in participants 16 years and older with advanced solid tumors with BRAF alterations. *J Clin Oncol* 2023; 41(Suppl. 16): TPS3164.

170. Zheng G, Tseng LH, Chen G, et al. Clinical detection and categorization of uncommon and concomitant mutations involving BRAF. *BMC Cancer* 2015; 15: 779.

171. Karoulia Z, Gavathiotis E and Poulikakos PI. New perspectives for targeting RAF kinase in human cancer. *Nat Rev Cancer* 2017; 17: 676–691.

172. Drilon AE, Hong DS, Tilburg CMv, et al. Long-term efficacy and safety of larotrectinib in a pooled analysis of patients with tropomyosin receptor kinase (TRK) fusion cancer. *J Clin Oncol* 2022; 40 (Suppl. 16): 3100.

173. Lu S, De Braud FGM, Fan Y, et al. 666P Updated efficacy and safety data of entrectinib in patients (pts) with locally advanced/metastatic NTRK fusion-positive (fp) solid tumours. *Ann Oncol* 2023; 34: S468–S469.

174. Cho BC, Doebele RC, Lin J, et al. MA11.07 Phase 1/2 TRIDENT-1 study of repotrectinib in patients with ROS1+ or NTRK+ advanced solid tumors. *J Thorac Oncol* 2021; 16 (Suppl. 3): S174–S175.

175. U.S. Food and Drug Administration. *FDA approves larotrectinib for solid tumors with NTRK gene fusions*, https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions (2018, accessed 30 November 2023).

176. Virgil H. Repotrectinib granted breakthrough therapy designation by FDA for solid tumors with NTRK gene fusion, https://www.cancernetwork.com/view/repotrectinib-granted-breakthrough-therapy-designation-by-fda-for-solid-tumors-with-ntrk-gene-fusion (2021, accessed 30 November 2023).

177. Middleton G, Fletcher P, Popat S, et al. The national lung matrix trial of personalized therapy in lung cancer. *Nature* 2020; 583: 807–812.

178. Camidge DR, Otterson GA, Clark JW, et al. Crizotinib in patients (pts) with MET-amplified non-small cell lung cancer (NSCLC): updated safety and efficacy findings from a phase 1 trial. *J Clin Oncol* 2018; 36(Suppl. 15): 9062.

179. Coleman N, Wei Z, Hong DS, et al. Phase II study of crizotinib in patients with MET amplification and MET exon 14 deletion: results from NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocols C1 and C2. *J Clin Oncol* 2023; 41(Suppl. 16): 3108.

180. Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat Med* 2020; 26: 47–51.

181. Verkerk K, van der Wel T, Zeverijn LJ, et al. 1392P Safety and efficacy of crizotinib in MET mutated (METmut) advanced non-small cell lung Cancer (aNSCLC): results from the Drug

Rediscovery Protocol (DRUP). *Ann Oncol* 2023; 34: S797.

182. Drilon AE, Camidge DR, Ou S-HI, et al. Efficacy and safety of crizotinib in patients (pts) with advanced MET exon 14-altered non-small cell lung cancer (NSCLC). *J Clin Oncol* 2016; 34(Suppl. 15): 108.

183. Park K, Chang GC, Curigliano G, et al. Phase I results of S49076 plus gefitinib in patients with EGFR TKI-resistant non-small cell lung cancer harbouring MET/AXL dysregulation. *Lung Cancer* 2021; 155: 127–135.

184. Schuler M, Berardi R, Lim WT, et al. Molecular correlates of response to capmatinib in advanced non-small-cell lung cancer: clinical and biomarker results from a phase I trial. *Ann Oncol* 2020; 31: 789–797.

185. Wolf J, Heist R, Kim T, et al. 994P Efficacy and safety of capmatinib plus spartalizumab in treatment-naïve patients with advanced NSCLC harboring MET exon 14 skipping mutation. *Ann Oncol* 2022; 33: S1007–S1008.

186. Lu S, Fang J, Li X, et al. Phase II study of savolitinib in patients (pts) with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations (METex14+). *J Clin Oncol* 2020; 38(Suppl. 15): 9519.

187. Wang Y, Liu T, Chen G, et al. Phase Ia/Ib study of the selective met inhibitor, savolitinib, in patients with advanced solid tumors: safety, efficacy, and biomarkers. *Oncologist* 2022; 27: 342.e83.

188. Chen H-J, Yang J-J, Yang X, et al. A phase I clinical trial to assess the safety, pharmacokinetics, and antitumor activity of glumetinib (SCC244) in patients with advanced non-small cell lung cancers (NSCLCs). *J Clin Oncol* 2020; 38(Suppl. 15): e21702.

189. Lu S, Yu Y, Zhou J, et al. Abstract CT034: phase II study of SCC244 in NSCLC patients harboring MET exon 14 skipping (METex14) mutations (GLORY study). *Cancer Res* 2022; 82(Suppl. 12): CT034.

190. Yang J, Zhou Q, Chen H, et al. Abstract CT127: a phase I study of cMET inhibitor bozitinib in patients with advanced NSCLC harboring cMET alterations. *Cancer Res* 2020; 80(Suppl. 16): CT127.

191. Lee DH, Han J-Y, Lemech CR, et al. ABN401 in patients with NSCLC with MET exon 14 (METex14) skipping: result from the pilot expansion study. *J Clin Oncol* 2023; 41(Suppl. 16): e21148.

192. Angevin E, Spitaleri G, Rodon J, et al. A first-in-human phase I study of SAR125844, a selective MET tyrosine kinase inhibitor, in patients with advanced solid tumours with MET amplification. *Eur J Cancer* 2017; 87: 131–139.

193. Pruis MA, Krebs MG, Plummer R, et al. A phase I trial of the dual MET kinase/OCT-2 inhibitor OMO-1 in metastatic solid malignancies including MET exon 14 mutated lung cancer. *Oncologist* 2023; 28: e1248–e1258.

194. Kishi K, Sakai H, Seto T, et al. First-line onartuzumab plus erlotinib treatment for patients with MET-positive and EGFR mutation-positive non-small-cell lung cancer. *Cancer Treat Res Commun* 2019; 18: 100113.

195. Camidge DR, Moran T, Demedts I, et al. A randomized, open-label phase II study evaluating emibetuzumab plus erlotinib and emibetuzumab monotherapy in MET immunohistochemistry positive NSCLC patients with acquired resistance to erlotinib. *Clin Lung Cancer* 2022; 23: 300–310.

196. Camidge DR, Janku F, Martinez-Bueno A, et al. Safety and preliminary clinical activity of the MET antibody mixture, Sym015 in advanced non-small cell lung cancer (NSCLC) patients with MET amplification/exon 14 deletion (METAmp/Ex14Δ). *J Clin Oncol* 2020; 38(Suppl. 15): 9510.

197. Kim D, Lee S, Jang I, et al. 998P A phase I study of CKD-702, an EGFR-cMET bispecific antibody, in advanced or metastatic non-small cell lung cancer (NSCLC). *Ann Oncol* 2022; 33: S1010.

198. Camidge DR, Barlesi F, Goldman JW, et al. Phase Ib study of telisotuzumab vedotin in combination with erlotinib in patients with c-MET protein-expressing non-small-cell lung cancer. *J Clin Oncol* 2023; 41: 1105–1115.

199. Broderick JM. FDA Grants crizotinib breakthrough designation for MET+ NSCLC and ALK+ ALCL, https://www.onclive.com/view/fda-grants-crizotinib-breakthrough-designation-for-met-nsclc-and-alk-alcl (2018, accessed 18 December 2023).

200. U.S. Food and Drug Administration. FDA D.I.S.C.O. Burst edition: FDA approvals of Tabrecta (capmatinib) for metastatic non-small cell lung cancer and Enhertu (fam-trastuzumab deruxtecan-nxki) for HER2-mutant non-small cell lung cancer, https://www.fda.gov/drugs/resources-information-approved-drugs/

fda-disco-burst-edition-fda-approvals-tabrecta-capmatinib-metastatic-non-small-cell-lung-cancer-and (2022, accessed 4 December 2023).

201. U.S. Food and Drug Administration. *FDA grants accelerated approval to tepotinib for metastatic non-small cell lung cancer*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tepotinib-metastatic-non-small-cell-lung-cancer (2021, accessed 18 December 2023).
202. Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol* 2016; 17: 1653–1660.
203. Nokihara H, Nishio M, Yamamoto N, et al. Phase 1 study of cabozantinib in Japanese patients with expansion cohorts in non-small-cell lung cancer. *Clin Lung Cancer* 2019; 20: e317–e328.
204. Yoh K, Seto T, Satouchi M, et al. 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* 2017; 5: 42–50.
205. Lee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. *Ann Oncol* 2017; 28: 292–297.
206. Gainor JF, Gadgeel S, Ou SI, et al. A Phase II study of the multikinase inhibitor ponatinib in patients with advanced, RET-rearranged NSCLC. *JTO Clin Res Rep* 2020; 1: 100045.
207. Hida T, Velcheti V, Reckamp KL, et al. A phase 2 study of lenvatinib in patients with RET fusion-positive lung adenocarcinoma. *Lung Cancer* 2019; 138: 124–130.
208. Yoh K, Seto T, Satouchi M, et al. Final survival results for the LURET phase II study of vandetanib in previously treated patients with RET-rearranged advanced non-small cell lung cancer. *Lung Cancer* 2021; 155: 40–45.
209. Gainor JF, Curigliano G, Kim DW, et al. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. *Lancet Oncol* 2021; 22: 959–969.
210. U.S. Food and Drug Administration. *FDA approves selpercatinib for lung and thyroid cancers with RET gene mutations or fusions*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions (2020, accessed 19 December 2023).
211. U.S. Food and Drug Administration. FDA D.I.S.C.O. Burst Edition: FDA approvals of Retevmo (selpercatinib) for adult patients with locally advanced or metastatic RET fusion-positive solid tumors, and Retevmo (selpercatinib) for adult patients with locally advanced or metastatic RET fusion-positive non-small cell lung cancer, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approvals-retevmo-selpercatinib-adult-patients-locally-advanced-or (2022, accessed 19 December 2023).
212. U.S. Food and Drug Administration. *FDA approves pralsetinib for non-small cell lung cancer with RET gene fusions*, https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pralsetinib-non-small-cell-lung-cancer-ret-gene-fusions (2023, accessed 19 December 2023).
213. Dziadziuszko R, Smit EF, Dafni U, et al. 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* 2019; 14: 1086–1094.
214. Zhou C, Li X, Wang Q, et al. Pyrotinib in HER2-mutant advanced lung adenocarcinoma after platinum-based chemotherapy: a multicenter, open-label, single-arm, phase II study. *J Clin Oncol* 2020; 38: 2753–2761.
215. Fan Y, Chen J, Zhou C, et al. Afatinib in patients with advanced non-small cell lung cancer harboring HER2 mutations, previously treated with chemotherapy: a phase II trial. *Lung Cancer* 2020; 147: 209–213.
216. Gandhi L, Bahleda R, Tolaney SM, et al. Phase I study of neratinib in combination with temsirolimus in patients with human epidermal growth factor receptor 2-dependent and other solid tumors. *J Clin Oncol* 2014; 32: 68–75.
217. Kim TM, Lee K-W, Oh D-Y, et al. Phase 1 studies of poziotinib, an irreversible pan-HER tyrosine kinase inhibitor in patients with advanced solid tumors. *Cancer Res Treat* 2018; 50: 835.
218. Kris M, Camidge D, Giaccone G, et al. 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* 2015; 26: 1421–1427.
219. De Grève J, Moran T, Graas M-P, et al. Phase II study of afatinib, an irreversible ErbB family blocker, in demographically and genotypically defined lung adenocarcinoma. *Lung Cancer* 2015; 88: 63–69.

220. Liu S, Villaruz L, Lee V, et al. LBA61 First analysis of RAIN-701: study of tarloxotinib in patients with non-small cell lung cancer (NSCLC) EGFR Exon 20 insertion, HER2-activating mutations & other solid tumours with NRG1/ERBB gene fusions. *Ann Oncol* 2020; 31: S1189.

221. Wang Y, Jiang T, Qin Z, et al. HER2 exon 20 insertions in non-small-cell lung cancer are sensitive to the irreversible pan-HER receptor tyrosine kinase inhibitor pyrotinib. *Ann Oncol* 2019; 30: 447–455.

222. Heymach J, Opdam F, Barve M, et al. A phase I, open-label, dose confirmation, escalation, and expansion trial of BI 1810631 as monotherapy in patients with advanced or metastatic solid tumors with HER2 aberrations. *Clin Lung Cancer* 2023; 24: e65–e68.

223. Bayer. Bayer receives U.S. FDA Breakthrough Therapy designation for BAY 2927088 for non-small cell lung cancer harboring HER2 activating mutations, https://www.bayer.com/media/en-us/bayer-receives-us-fda-breakthrough-therapy-designation-for-bay-2927088-for-non-small-cell-lung-cancer-harboring-her2-activating-mutations/ (2024, accessed 3 May 2024).

224. Gatzemeier U, Groth G, Butts C, et al. Randomized phase II trial of gemcitabine–cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. *Ann Oncol* 2004; 15: 19–27.

225. Zinner RG, Glisson BS, Fossella FV, et al. Trastuzumab in combination with cisplatin and gemcitabine in patients with Her2-overexpressing, untreated, advanced non-small cell lung cancer: report of a phase II trial and findings regarding optimal identification of patients with Her2-overexpressing disease. *Lung Cancer* 2004; 44: 99–110.

226. Lara PN Jr., Laptalo L, Longmate J, et al. Trastuzumab plus docetaxel in HER2/neu-positive non-small-cell lung cancer: a California Cancer Consortium screening and phase II trial. *Clin Lung Cancer* 2004; 5: 231–236.

227. Krug LM, Miller VA, Patel J, et al. Randomized phase II study of weekly docetaxel plus trastuzumab versus weekly paclitaxel plus trastuzumab in patients with previously untreated advanced nonsmall cell lung carcinoma. *Cancer* 2005; 104: 2149–2155.

228. Meric-Bernstam F, Hainsworth J, Bose R, et al. MyPathway HER2 basket study: pertuzumab (P) + trastuzumab (H) treatment of a large, tissue-agnostic cohort of patients with HER2-positive advanced solid tumors. *J Clin Oncol* 2021; 39(Suppl. 15): 3004.

229. Peters S, Stahel R, Bubendorf L, et al. Trastuzumab emtansine (T-DM1) in patients with previously treated HER2-overexpressing metastatic non–small cell lung cancer: efficacy, safety, and biomarkers. *Clin Cancer Res* 2019; 25: 64–72.

230. Hotta K, Aoe K, Kozuki T, et al. A phase II study of trastuzumab emtansine in HER2-positive non-small cell lung cancer. *J Thorac Oncol* 2018; 13: 273–279.

231. Thavaneswaran S, Mersiades A, Lin FP-Y, et al. Trastuzumab emtansine (T-DM1) in advanced cancers with HER2 mutations or amplification: results from the molecular screening and therapeutics (MoST) program substudy. *J Clin Oncol* 2023; 41(Suppl. 16): 3127.

232. Tsurutani J, Iwata H, Krop I, et al. Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, phase I study in multiple advanced solid tumors. *Cancer Discov* 2020; 10: 688–701.

233. AstraZeneca. Enhertu granted Breakthrough Therapy Designation in the US for HER2-mutant metastatic non-small cell lung cancer, https://www.astrazeneca.com/media-centre/press-releases/2020/enhertu-granted-breakthrough-therapy-designation-in-the-us-for-her2-mutant-metastatic-non-small-cell-lung-cancer.html (2020, accessed 10 January 2024).

234. U.S. Food and Drug Administration. *FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-mutant non-small cell lung cancer*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-her2-mutant-non-small-cell-lung (2022, accessed 10 January 2024).

235. Taniguchi H, Yagisawa M, Satoh T, et al. Tissue-agnostic efficacy of trastuzumab deruxtecan (T-DXd) in advanced solid tumors with HER2 amplification identified by plasma cell-free DNA (cfDNA) testing: results from a phase 2 basket trial (HERALD/EPOC1806). *J Clin Oncol* 2023; 41(Suppl. 16): 3014.

236. Hurvitz SA, Park H, Frentzas S, et al. Safety and unique pharmacokinetic profile of ARX788, a site-specific ADC, in heavily pretreated patients with HER2-overexpresing solid tumors: results from two phase 1 clinical trials. *J Clin Oncol* 2021; 39(Suppl. 15): 1038.

237. Zhang J, Liu R, Gao S, et al. Phase I study of A166, an antibody–drug conjugate in advanced

HER2-expressing solid tumours. *NPJ Breast Cancer* 2023; 9: 28.

238. Gong J, Chen L, Sun M, et al. Efficacy and safety of KN026 in combination with KN046 in patients with locally advanced unresectable or metastatic HER2-positive other solid tumors. *J Clin Oncol* 2023; 41(Suppl. 16): 3621.

239. Riely GJ, Johnson ML, Medina C, et al. A phase II trial of Salirasib in patients with lung adenocarcinomas with KRAS mutations. *J Thorac Oncol* 2011; 6: 1435–1437.

240. Minchom AR, Perez VS, Morton C, et al. Phase I trial of the RAF/MEK clamp VS-6766 in combination with everolimus using an intermittent schedule with expansion in NSCLC across multiple KRAS variants. *J Clin Oncol* 2022; 40(Suppl. 16): 9018.

241. Sullivan RJ, Infante JR, Janku F, et al. 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* 2018; 8: 184–195.

242. Saltos AN, Creelan BC, Tanvetyanon T, et al. A phase I/IB trial of binimetinib in combination with erlotinib in NSCLC harboring activating KRAS or EGFR mutations. *Lung Cancer* 2023; 183: 107313.

243. Froesch P, Mark M, Rothschild SI, et al. Binimetinib, pemetrexed and cisplatin, followed by maintenance of binimetinib and pemetrexed in patients with advanced non-small cell lung cancer (NSCLC) and KRAS mutations. The phase 1B SAKK 19/16 trial. *Lung Cancer* 2021; 156: 91–99.

244. Blumenschein GR Jr, Smit EF, Planchard D, et al. A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC). *Ann Oncol* 2015; 26: 894–901.

245. Tolcher AW, Khan K, Ong M, et al. Antitumor activity in RAS-driven tumors by blocking AKT and MEK. *Clin Cancer Res* 2015; 21: 739–748.

246. Fung AS, Graham DM, Chen EX, et al. A phase I study of binimetinib (MEK 162), a MEK inhibitor, plus carboplatin and pemetrexed chemotherapy in non-squamous non-small cell lung cancer. *Lung Cancer* 2021; 157: 21–29.

247. Arbour KC, Manchado E, Bott MJ, et al. Phase 1 clinical trial of trametinib and ponatinib in patients with NSCLC harboring KRAS mutations. *JTO Clin Res Rep* 2022; 3: 100256.

248. Aggarwal C, Maity AP, Bauml JM, et al. A phase II open-label trial of binimetinib and hydroxychloroquine in patients with advanced KRAS-mutant non-small cell lung cancer. *Oncologist* 2023; 28: 644.e564.

249. Han B and Zou B. P1.11-02 Combined regimen of anlotinib and trametinib for NSCLC patients harbouring Pan-KRAS mutation without KRASG12C. *J Thorac Oncol* 2022; 17(Suppl. 9): S110.

250. Corcoran R, Do K, Cleary J, et al. 664P Final results of a phase I/II study of combined BCL-xL and MEK inhibition with navitoclax and trametinib in KRAS or NRAS mutant advanced solid tumors. *Ann Oncol* 2023; 34: S467.

251. Han J, Liu Y, Yang S, et al. MEK inhibitors for the treatment of non-small cell lung cancer. *J Hematol Oncol* 2021; 14: 1.

252. Goldman JW, Mazieres J, Barlesi F, et al. A randomized phase III study of abemaciclib versus erlotinib in patients with stage IV non-small cell lung cancer with a detectable KRAS mutation who failed prior platinum-based therapy: JUNIPER. *Front Oncol* 2020; 10: 578756.

253. Patnaik A, Rosen LS, Tolaney SM, et al. Efficacy and safety of abemaciclib, an inhibitor of CDK4 and CDK6, for patients with breast cancer, non-small cell lung cancer, and other solid tumors. *Cancer Discov* 2016; 6: 740–753.

254. Pujol J-L, Vansteenkiste JF, Paz-Ares LG, et al. A phase Ib study of abemaciclib in combination with pembrolizumab for patients (pts) with stage IV Kirsten rat sarcoma mutant (KRAS-mut) or squamous non-small cell lung cancer (NSCLC) (NCT02779751): interim results. *J Clin Oncol* 2020; 38(Suppl. 15): 9562.

255. Veluswamy R, Bhalla S, Samstein R, et al. 1018P phase I/II trial of rigosertib and nivolumab for KRAS mutated non-small cell lung cancer (NSCLC) patients. *Ann Oncol* 2022; 33: S1019–S1020.

256. Lietman CD, Johnson ML, McCormick F, et al. More to the RAS story: KRASG12C inhibition, resistance mechanisms, and moving beyond KRASG12C. *Am Soc Clin Oncol Educ Book* 2022; 42: 205–217.

257. Fell JB, Fischer JP, Baer BR, et al. Discovery of tetrahydropyridopyrimidines as irreversible covalent inhibitors of KRAS-G12C with in vivo activity. *ACS Med Chem Lett* 2018; 9: 1230–1234.

258. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med* 2021; 384: 2371–2381.

259. Molina-Arcas M and Downward J. Exploiting the therapeutic implications of KRAS inhibition on tumor immunity. *Cancer Cell* 2024; 42: 338–357.

260. U.S. Food and Drug Administration. *FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sotorasib-kras-g12c-mutated-nsclc (2021, accessed 11 January 2024).

261. U.S. Food and Drug Administration. *FDA grants accelerated approval to adagrasib for KRAS G12C-mutated NSCLC*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-adagrasib-kras-g12c-mutated-nsclc (2022, accessed 11 January 2024).

262. Paz-Ares L, Mehta B, Wang Y, et al. Sotorasib in KRASG12C mutated lung cancer—authors' reply. *Lancet* 2024; 403: 145–146.

263. Oncologic Drugs Advisory Committee – U.S. Food and Drug Administration. October 5, 2023: Meeting of the Oncologic Drugs Advisory Committee Meeting Announcement – Meeting Materials, https://www.fda.Gov/advisory-committees/advisory-committee-calendar/october-5-2023-meeting-oncologic-drugs-advisory-committee-meeting-announcement-10052023#event-materials (2023, accessed 11 January 2024).

264. Wang J, Martin-Romano P, Cassier P, et al. Phase I study of JNJ-74699157 in patients with advanced solid tumors harboring the KRAS G12C mutation. *Oncologist* 2022; 27: 536.e53.

265. Zhang Y, Zhou L, Gong Y, et al. Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of GEC255, a novel KRASG12C inhibitor, in advanced solid tumors. *J Clin Oncol* 2023; 41(Suppl. 16): 9112.

266. Liu R, Qu X, Yang N, et al. First-in-human study of ZG19018, targeting KRAS G12C, as monotherapy in patients with advanced solid tumors. *J Clin Oncol* 2023; 41(Suppl. 16): e15127.

267. Li J, Zhao J, Cao B, et al. A phase I/II study of first-in-human trial of JAB-21822 (KRAS G12C inhibitor) in advanced solid tumors. *J Clin Oncol* 2022; 40(Suppl. 16): 3089.

268. Zhou Q, Yang N, Zhao J, et al. Phase I dose-escalation study of IBI351 (GFH925) monotherapy in patients with advanced solid tumors. *J Clin Oncol* 2022; 40(Suppl. 16): 3110.

269. Rojas C, Lugowska I, Juergens R, et al. 663P Safety and preliminary efficacy of the KRAS G12C Inhibitor MK-1084 in solid tumors and in combination with pembrolizumab in NSCLC. *Ann Oncol* 2023; 34: S466.

270. Pacini L, Jenks AD, Lima NC, et al. Targeting the fibroblast growth factor receptor (FGFR) family in lung cancer. *Cells* 2021; 10: 1154.

271. Ng TL, Yu H, Smith DE, et al. Preselection of lung cancer cases using FGFR1 mRNA and gene copy number for treatment with ponatinib. *Clin Lung Cancer* 2019; 20: e39–e51.

272. Lim SH, Sun JM, Choi YL, et al. Efficacy and safety of dovitinib in pretreated patients with advanced squamous non-small cell lung cancer with FGFR1 amplification: a single-arm, phase 2 study. *Cancer* 2016; 122: 3024–3031.

273. Jones RL, Ratain MJ, O'Dwyer PJ, et al. Phase II randomised discontinuation trial of brivanib in patients with advanced solid tumours. *Eur J Cancer* 2019; 120: 132–139.

274. Paik PK, Shen R, Berger MF, et al. A phase Ib open-label multicenter study of AZD4547 in patients with advanced squamous cell lung cancers. *Clin Cancer Res* 2017; 23: 5366–5373.

275. Aggarwal C, Redman MW, Lara PN Jr, et al. SWOG S1400D (NCT02965378), a phase II study of the fibroblast growth factor receptor inhibitor AZD4547 in previously treated patients with fibroblast growth factor pathway-activated stage IV squamous cell lung cancer (lung-MAP substudy). *J Thorac Oncol* 2019; 14: 1847–1852.

276. Schuler M, Cho BC, Sayehli CM, et al. Rogaratinib in patients with advanced cancers selected by FGFR mRNA expression: a phase 1 dose-escalation and dose-expansion study. *Lancet Oncol* 2019; 20: 1454–1466.

277. Nogova L, Sequist LV, Perez Garcia JM, et al. Evaluation of BGJ398, a fibroblast growth factor receptor 1-3 kinase inhibitor, in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors: results of a global phase I, dose-escalation and dose-expansion study. *J Clin Oncol* 2017; 35: 157–165.

278. Pant S, Schuler MH, Iyer G, et al. Tumor agnostic efficacy and safety of erdafitinib (erda) in patients (pts) with advanced solid tumors with prespecified FGFR alterations (FGFRalt):

RAGNAR primary analysis. *J Clin Oncol* 2023; 41(Suppl. 16): 3121.

279. Addeo A, Rothschild SI, Holer L, et al. Fibroblast growth factor receptor (FGFR) inhibitor rogaratinib in patients with advanced pretreated squamous-cell non-small cell lung cancer over-expressing FGFR mRNA: the SAKK 19/18 phase II study. *Lung Cancer* 2022; 172: 154–159.

280. Decoster L, Aftimos P, Rottey S, et al. 201P Afatinib for EGFR, HER2 or HER3 mutated solid tumors: a phase II Belgian precision study. *Ann Oncol* 2023; 34: S262.

281. Schram AM, Ahnert JR, Patel MR, et al. Safety and preliminary efficacy from the phase 1 portion of MasterKey-01: a first-in-human dose-escalation study to determine the recommended phase 2 dose (RP2D), pharmacokinetics (PK) and preliminary antitumor activity of BDTX-189, an inhibitor of allosteric ErbB mutations, in patients (pts) with advanced solid malignancies. *J Clin Oncol* 2021; 39(Suppl. 15): 3086.

282. Salawu A, Hansen AR, Spreafico A, et al. A phase 2 trial of afatinib in patients with solid tumors that harbor genomic aberrations in the HER family: the MOBILITY3 Basket Study. *Target Oncol* 2022; 17: 271–281.

283. Yonesaka K, Hirotani K, von Pawel J, et al. Circulating heregulin level is associated with the efficacy of patritumab combined with erlotinib in patients with non-small cell lung cancer. *Lung Cancer* 2017; 105: 1–6.

284. Paz-Arez L, Serwatowski P, Szczęsna A, et al. P3.02b-045 patritumab plus erlotinib in EGFR wild-type advanced non-small cell lung cancer (NSCLC): part a results of HER3-lung study: topic: EGFR clinical. *J Thorac Oncol* 2017; 12(Suppl. 1): S1214–S1215.

285. Sequist LV, Janne PA, Huber RM, et al. SHERLOC: a phase 2 study of MM-121 plus with docetaxel versus docetaxel alone in patients with heregulin (HRG) positive advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2019; 37(Suppl. 15): 9036.

286. Meulendijks D, Jacob W, Voest EE, et al. Phase Ib study of lumretuzumab plus cetuximab or erlotinib in solid tumor patients and evaluation of HER3 and heregulin as potential biomarkers of clinical activity. *Clin Cancer Res* 2017; 23: 5406–5415.

287. Cejalvo JM, Jacob W, Fleitas Kanonnikoff T, et al. A phase Ib/II study of HER3-targeting lumretuzumab in combination with carboplatin and paclitaxel as first-line treatment in patients with advanced or metastatic squamous non-small cell lung cancer. *ESMO Open* 2019; 4: e000532.

288. Sequist LV, Gray JE, Harb WA, et al. Randomized phase II trial of seribantumab in combination with erlotinib in patients with EGFR wild-type non-small cell lung cancer. *Oncologist* 2019; 24: 1095–1102.

289. Gan HK, Millward M, Jalving M, et al. A phase I, first-in-human study of GSK2849330, an anti-HER3 monoclonal antibody, in HER3-expressing solid tumors. *Oncologist* 2021; 26: e1844–e1853.

290. Carrizosa DR, Burkard ME, Elamin YY, et al. CRESTONE: initial efficacy and safety of seribantumab in solid tumors harboring NRG1 fusions. *J Clin Oncol* 2022; 40(Suppl. 16): 3006.

291. Rosa K. FDA grants priority review to zenocutuzumab BLA for NRG1+ NSCLC and pancreatic cancer, https://www.onclive.com/view/fda-grants-priority-review-to-zenocutuzumab-bla-for-nrg1-nsclc-and-pancreatic-cancer (2024, accessed 29 May 2024).

292. Pelosci A. FDA grants fast track designation of seribantumab for NRG1+ advanced solid tumors, https://www.cancernetwork.com/view/fda-grants-fast-track-designation-of-seribantumab-for-nrg1-advanced-solid-tumors (2022, accessed 29 May 2024).

293. Vansteenkiste JF, Canon JL, De Braud F, et al. Safety and efficacy of buparlisib (BKM120) in patients with PI3K pathway-activated non-small cell lung cancer: results from the phase II BASALT-1 study. *J Thorac Oncol* 2015; 10: 1319–1327.

294. Langer CJ, Redman MW, Wade JL 3rd, et al. SWOG S1400B (NCT02785913), a phase II study of GDC-0032 (taselisib) for previously treated PI3K-positive patients with stage IV squamous cell lung cancer (lung-MAP sub-study). *J Thorac Oncol* 2019; 14: 1839–1846.

295. Lung Cancer Research Foundation. FDA approvals in lung cancer treatment, https://www.lungcancerresearchfoundation.org/research/why-research/treatment-advances/ (2023, accessed 7 February 2024).

296. U.S. Food and Drug Administration. *FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dabrafenib-combination-trametinib-unresectable-or-metastatic-solid (2022, accessed 7 February 2024).

297. U.S. Food and Drug Administration. *FDA approves selpercatinib for locally advanced or metastatic RET fusion-positive solid tumors*, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-locally-advanced-or-metastatic-ret-fusion-positive-solid-tumors (2022, accessed 7 February 2024).

298. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol* 2018; 29: 1895–1902.

299. Cho D, Lord SJ, Ward R, et al. Criteria for assessing evidence for biomarker-targeted therapies in rare cancers-an extrapolation framework. *Ther Adv Med Oncol* 2024; 16: 17588359241273062.

300. Lam TC, Cho WC, Au JS, et al. Consensus statements on precision oncology in the China Greater Bay Area. *JCO Precis Oncol* 2023; 7: e2200649.

301. Lebedeva AA, Kavun AI, Veselovsky EM, et al. CRAC (clinical relevance of alterations in cancer): a knowledge base for the selection of molecularly matched therapy for solid tumors. *Sovrem Tekhnologii Med* 2022; 14: 15–23.

302. Westphalen CB, Martins-Branco D, Beal JR, et al. The ESMO tumour-agnostic classifier and screener (ETAC-S): a tool for assessing tumour-agnostic potential of molecularly guided therapies and for steering drug development. *Ann Oncol* 2024; 35: 936–953.

303. Tibau A, Hwang TJ, Molto C, et al. Clinical value of molecular targets and FDA-approved genome-targeted cancer therapies. *JAMA Oncol* 2024; 10: 634–641.

304. Crimini E, Repetto M, Tarantino P, et al. Challenges and obstacles in applying therapeutical indications formulated in molecular tumor boards. *Cancers* 2022; 14: 3193.

305. Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research—FDA. Developing targeted therapies in low-frequency molecular subsets of a disease, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-targeted-therapies-low-frequency-molecular-subsets-disease (2018, accessed 12 November 2024).

306. Maggie Liu S-Y, Jin Z-Y, Deng J-Y, et al. Drug development and evidence for lung cancer targeted therapy in Eastern Asia. *Lancet Reg Health West Pac* 2024; 49: 101090.

307. Lu CY, Terry V and Thomas DM. Precision medicine: affording the successes of science. *NPJ Precis Oncol* 2023; 7: 3.

308. Weymann D, Pollard S, Lam H, et al. Toward best practices for economic evaluations of tumor-agnostic therapies: a review of current barriers and solutions. *Value Health* 2023; 26: 1608–1617.

309. Nagasaka M, Brazel D and Ou S-HI. Taletrectinib for the treatment of ROS-1 positive non-small cell lung cancer: a drug evaluation of phase I and II data. *Expert Opin Investig Drugs* 2024; 33: 79–84.

310. Xiang Y, Liu X, Wang Y, et al. Mechanisms of resistance to targeted therapy and immunotherapy in non-small cell lung cancer: promising strategies to overcoming challenges. *Front Immunol* 2024; 15: 1366260.

311. Cho BC, Simi A, Sabari J, et al. Amivantamab, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) bispecific antibody, designed to enable multiple mechanisms of action and broad clinical applications. *Clin Lung Cancer* 2023; 24: 89–97.

312. Feldt SL and Bestvina CM. The role of MET in resistance to EGFR inhibition in NSCLC: a review of mechanisms and treatment implications. *Cancers* 2023; 15: 2998.

313. Hotta K, Matsuo K, Ueoka H, et al. Addition of platinum compounds to a new agent in patients with advanced non-small-cell lung cancer: a literature based meta-analysis of randomised trials. *Ann Oncol* 2004; 15: 1782–1789.

314. Sheng M, Zhao Y, Wang F, et al. Targeted drugs for unselected patients with advanced non-small-cell lung cancer: a network meta-analysis. *J Thorac Dis* 2016; 8: 98–115.

315. Liu L, Bai H, Wang C, et al. Efficacy and safety of first-line immunotherapy combinations for advanced NSCLC: a systematic review and network meta-analysis. *J Thorac Oncol* 2021; 16: 1099–1117.

316. Jiang L, Zhang J, Xu Y, et al. Treating non-small cell lung cancer by targeting the PI3K signaling pathway. *Chin Med J* 2022; 135: 1272–1284.

317. Sanaei MJ, Razi S, Pourbagheri-Sigaroodi A, et al. The PI3K/Akt/mTOR pathway in lung cancer; oncogenic alterations, therapeutic opportunities, challenges, and a glance at the

application of nanoparticles. *Transl Oncol* 2022; 18: 101364.

318. Sirico M, D'Angelo A, Gianni C, et al. Current state and future challenges for PI3K inhibitors in cancer therapy. *Cancers* 2023; 15: 703.

319. Fruman DA and Rommel C. PI3K and cancer: lessons, challenges and opportunities. *Nat Rev Drug Discov* 2014; 13: 140–156.

320. Sivakumar S, Jin DX, Rathod R, et al. Genetic heterogeneity and tissue-specific patterns of tumors with multiple PIK3CA mutations. *Clin Cancer Res* 2023; 29: 1125–1136.

321. Scheffler M, Bos M, Gardizi M, et al. PIK3CA mutations in non-small cell lung cancer (NSCLC): genetic heterogeneity, prognostic impact and incidence of prior malignancies. *Oncotarget* 2015; 6: 1315–1326.

322. Daher S, Zer A, Tschernichovsky R, et al. Driver mutation characteristics of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) in advanced non-small cell lung cancer. *Lung Cancer* 2023; 178: 229–236.

323. Yap TA, Dumbrava EE, Ahnert JR, et al. First-in-human biomarker-driven phase I trial of the potent and selective glutaminase-1 (GLS1) inhibitor IACS-6274 (IPN60090) in patients (pts) with molecularly selected advanced solid tumors. *J Clin Oncol* 2021; 39(Suppl. 15): 3001.

324. Riess J, Frankel P, Massarelli E, et al. MA13.08 a phase 1 trial of sapanisertib and telaglenastat (CB-839) in patients with advanced NSCLC (NCI 10327): results from dose escalation. *J Thorac Oncol* 2022; 17(Suppl. 9): S91–S92.

325. Hellyer JA, Padda SK, Diehn M, et al. Clinical implications of KEAP1-NFE2L2 mutations in NSCLC. *J Thorac Oncol* 2021; 16: 395–403.

326. Papadopoulos KP, Bruno D, Kitazono S, et al. OA05.06 Datopotamab deruxtecan (Dato-DXd) + durvalumab ± carboplatin in advanced/mNSCLC: initial results from phase 1b TROPION-lung04. *J Thorac Oncol* 2023; 18(Suppl. 11): S55.

327. Gilead. Gilead's phase 2 EVOKE-02 study of Trodelvy (sacituzumab govitecan-hziy) in combination with KEYTRUDA (pembrolizumab) demonstrates promising clinical activity in first-line metastatic non-small cell lung cancer, https://www.gilead.com/news-and-press/press-room/press-releases/2023/9/gileads-phase-2-evoke02-study-of-trodelvy-sacituzumab-govitecanhziy-in-combination-with-keytruda-pembrolizumab-demonstrates-promising-clinica (2023, accessed 7 February 2024).

328. Lisberg AE, Sands J, Shimizu T, et al. Dose escalation and expansion from the phase I study of DS-1062, a trophoblast cell-surface antigen 2 (TROP2) antibody drug conjugate (ADC), in patients (pts) with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2020; 38(Suppl. 15): 9619.

329. Ahn MJ, Lisberg A, Paz-Ares L, et al. LBA12 datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase III study TROPION-Lung01. *Ann Oncol* 2023; 34: S1305–S1306.

330. Fang W, Cheng Y, Chen Z, et al. SKB264 (TROP2-ADC) for the treatment of patients with advanced NSCLC: efficacy and safety data from a phase 2 study. *J Clin Oncol* 2023; 41(Suppl. 16): 9114.

331. Heist RS, Guarino MJ, Masters G, et al. Therapy of advanced non-small-cell lung cancer with an SN-38-anti-trop-2 drug conjugate, sacituzumab govitecan. *J Clin Oncol* 2017; 35: 2790–2797.

332. Liu X, Deng J, Zhang R, et al. The clinical development of antibody-drug conjugates for non-small cell lung cancer therapy. *Front Immunol* 2023; 14: 1335252.

333. Coleman N, Yap TA, Heymach JV, et al. Antibody-drug conjugates in lung cancer: dawn of a new era? *NPJ Precis Oncol* 2023; 7: 5.

334. Rosner S, Valdivia A, Hoe HJ, et al. Antibody-drug conjugates for lung cancer: payloads and progress. *Am Soc Clin Oncol Educ Book* 2023; 43: e389968.