Targeted Oncology: A MAP to the Future of Targeted Oncology

February 12, 2026

Peter Bak, PhD
Back Bay Life Science Advisors

Anna Urrea
Back Bay Life Science Advisors

Geir H. Holom, PhD, MD, BSc
DNB Carnegie

Contact the authors:
healthcarepartnership@bblsa.com

Subscribe for our weekly healthcare market updates:
subscribe@bblsa.com

Targeted Oncology – Significance

- The mitogen-activated protein kinase (MAPK) pathway is one of the most commonly perturbed signaling pathways in human cancers; flowing from RAS to RAF to MEK to ERK, the pathway is a master regulator of cellular proliferation and survival; therefore, the amplification of proteins or mutation of key signaling domains are a common hallmark of cancer
- Given the importance of these targets, approved drugs within the space have posted impressive revenue:
  - Launched in 2015, the EGFR tyrosine kinase inhibitor, Tagrisso (osimertinib) has garnered AstraZeneca over $6B in revenue in 2024
  - Targeted agents for specific KRAS mutations: Krazati (adagrasib, BMS) and Lumakras (sotorasib, Amgen) have recently launched, each expecting to clear $500M in annual sales by 2030
- Nevertheless, there is still room for improvement along these paths, from addressing resistance mutations that arise to current therapies, developing drugs targeting specific mutations driving oncogenesis, to therapies that may cover more than one mutation in a given signaling node
- Each target is an active area of clinical development (e.g., 70 clinical stage programs EGFR and >50 clinical stage programs targeting KRAS); with large pharma players such as JnJ, Roche, Lilly, Merck recently launching and/or initiating Phase 3 programs in this space
  - Late 2025 and early 2026 has seen a spate of data readouts from Recursion, Immuneering, Oric, with critical data readouts expected from Revolution and Eli Lilly in the KRAS space
- This space continues to be an active area of deal making, with 198 relevant small-molecule targeted oncology deals executed since 2019; kinase programs account for 45% (89/198) of all deals
  - Most recently, AZ entered into a global exclusive licensing agreement with Jacobio Pharma in December 2025 for JAB-23E73, a Phase 1/2a pan-KRAS inhibitor, in a deal potentially worth over $2 billion
- Early-stage innovation in small molecule targeted chemistries has drawn investor and strategic interest from biopharma alike, particularly those focusing on novel chemical platforms to discover the next wave of targeted inhibitors
  - Next-generation chemistry platforms are attracting outsized capital, with Scorpion, Vividion, Terremoto, Frontier, and Alterome each raising >$200M privately
  - Large pharma has followed suit through headline transactions, including Bayer's $1.5B+ acquisition of Vividion and Lilly's up-to-$2.5B acquisition of Scorpion's STX-478
- Herein, we cover the commercial and development landscape across these pathways focusing on small molecule chemistry, assess the transactional space within targeted oncology, and evaluate the early-stage investment landscape for novel chemistry platforms

Targeted Oncology – Executive Summary (1 of 2)

The MAPK Pathway at the Crossroads of Cancer Signaling
The epidermal growth factor receptor (EGFR) and RAS–RAF–MEK–ERK (MAPK) cascade together to form one of the most frequently dysregulated signaling axes in solid tumors and remain a backbone of precision oncology. At the cell surface, EGFR and other receptor tyrosine kinases (RTKs) unleash a signaling cascade inside the cell upon binding to their cognate ligands. This chain reaction, mediated in part by serial activation of Ras GTPases, RAF kinases, MEK, and ERK, regulates cellular viability, differentiation, and replication. Given their importance in cellular homeostasis, tumor growth can occur when any of these players is mutated or altered: from EGFR amplification and overexpression to mutations in the RAS and RAF family of proteins. Similarly, molecules that block or inhibit their activity have posted impressive clinical results and garnered attractive commercial returns for pharma sponsors.

EGFR: An Established Blockbuster Market
EGFR was among the first nodes in this pathway to be clinically validated, with successive generations of tyrosine kinase inhibitors (TKIs) developed to address unmet needs: from development of resistance mutations to treatment of brain metastases. First-generation agents such as gefitinib and erlotinib demonstrated the value of EGFR targeting but were undermined by emergence of on-target resistance mutations and cross reactivity with unaffected EGFR. With second generation products, beginning to address escape mutations but harboring side effect profiles, the third-generation, mutant-selective TKI osimertinib (Tagrisso) has since become a global franchise, reaching ~$6.5B in worldwide sales in 2024 and establishing EGFR inhibition as a durable commercial pillar. Newer third-generation agents such as lazertinib (Lazcluze, CNS-penetrant; projected ~$1.2B by 2030) and sunvozertinib (the first approved oral exon-20 insertion inhibitor in the US, 2025) extend coverage to historically refractory mutation classes. Across preclinical–Phase III stages, 112 EGFR-targeted assets are in development, with 21 in Phase III, 24 in Phase II, 28 in Phase I, and 39 in preclinical studies; small molecules account for 83 of these programs, underscoring their continued centrality despite rising interest in biologics and degraders.

KRAS: From the Undruggable to the "Next Big Thing"
Further along the cascade, RAS proteins are commonly affected signaling proteins, with KRAS, the most commonly mutated RAS variant, emerging in less than a decade from an "undruggable" oncogene to a validated commercial target with a deep, diversified pipeline. First-generation KRAS G12C inhibitors, sotorasib (Lumakras) and adagrasib (Krazati), are each projected to exceed $500M in annual sales by 2030. Building on this, at least 126 KRAS-directed assets are in development, spanning ~71 preclinical, 32 Phase I, 19 Phase II, and 4 Phase III programs. Next-generation G12C inhibitors such as olomorasib, divarasib, and MK-1084 are now in Phase III, often in combination with PD-1 or EGFR antibodies, while novel inhibition approaches such as elironrasib aim to overcome resistance to earlier G12C agents. In parallel, clinical development has rapidly expanded into KRAS-G12D mutations and multi-allele or pan-KRAS and pan-RAS agents.

Targeted Oncology – Executive Summary (2 of 2)

RAF/MEK/ERK: Well-Established Targets Moving into New Markets
Inhibitors of downstream MAPK components (e.g., BRAF, MEK, and ERK) likewise yielded durable commercial franchises. Legacy BRAF/MEK combinations, particularly dabrafenib plus trametinib (Tafinlar/Mekinist), anchor treatment of BRAF V600–mutant melanoma and together generated nearly $3B in 2024 sales; Pfizer's encorafenib (Braftovi) and binimetinib (Mektovi) contributed a further ~$600M and ~$270M. Newer, more niche products are expanding the MAPK footprint into genetically defined rare diseases: Ojemda (tovorafenib) for BRAF-altered pediatric low-grade glioma and Gomekli (mirdametinib) for NF1-associated plexiform neurofibromas are each forecast to reach ~$1.0–1.2B in annual sales by 2032. Despite these successes, ERK reactivation leads to resistance in up to 40% of RAF/MEK-pretreated tumors, driving renewed interest in ERK1/2 and upstream/downstream combinations.

Deal Flow Accelerates
These scientific advances are mirrored by robust business development activity, heavily concentrated in kinase pathways like EGFR and MAPK. Since 2019, 198 relevant small-molecule targeted oncology deals have been executed, with an average of 52% of annual transactions occurring at the discovery or preclinical stage—highlighting strategic buyers' continued willingness to engage early in the value chain. Deal volume declined in 2022–2023 but rebounded sharply in 2024, when transactions exceeded pre-pandemic levels by ~33%; preclinical-stage deals drove much of this rebound, and ~25% involved major pharmas such as Merck, Bayer, and AstraZeneca. Consistent with this concentration, kinase targets account for 45% of all deals (89/198), and within kinases, MAPK pathway drivers represent ~30% of kinase deal activity—led by RAS/KRAS (10 deals), RAF/BRAF (7), EGFR (6), and MEK/ERK (4).

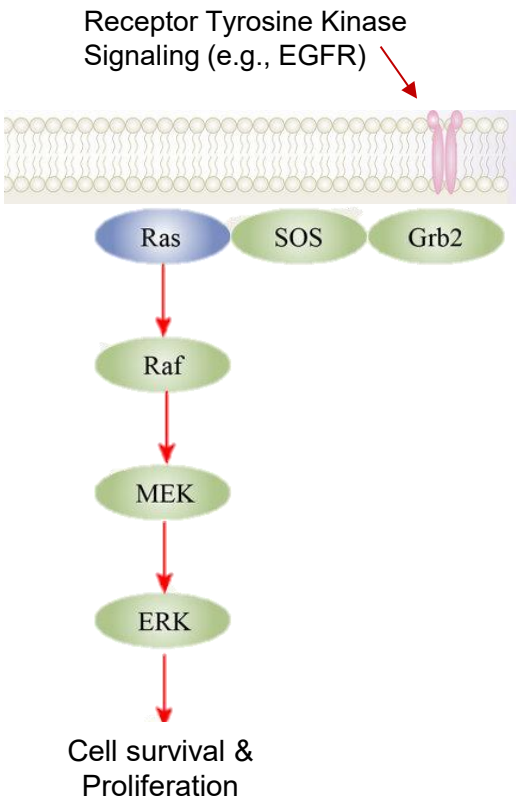
The Next Wave of Novel Chemistry
This surge of interest in covalent chemistry—particularly against EGFR and KRAS—has created a wave of platform innovation and capital formation. Modern covalent drugs were catalyzed by the 2013 approval of the BTK inhibitor ibrutinib soon followed by third-generation EGFR inhibitor osimertinib and the first covalent KRAS G12C agents. Today's toolkit spans irreversible covalent inhibitors, reversible covalent scaffolds, and chemoproteomics-enabled discovery that can map cysteine, lysine, and other nucleophilic residues across thousands of proteins in parallel. Venture investors have backed a cadre of dedicated covalent and chemoproteomics companies: five (Scorpion, Vividion, Terremoto, Frontier, Alterome) have each raised more than $200M, with Scorpion alone securing $420M, while additional platforms such as Enlaza, Totus, Exo, Matchpoint, BridGene, Rezo, Nexo, Hyku, Belharra, and others have raised $50–160M apiece. Large pharma has responded with sizeable alliances and acquisitions, including Bayer's $1.5B-plus acquisition of Vividion and Lilly's up-to-$2.5B acquisition of Scorpion's STX-478.

Collectively, the high mutational prevalence and dependence on the EGFR–RAS–MAPK axis, the multi-billion-dollar revenues of existing targeted therapies, the concentration of deal-making around MAPK kinases, and the rapid maturation of covalent technologies suggest this pathway will remain a central arena for innovation, partnering, and value creation in oncology

Introduction

Driver Mutations in Oncology

The EGFR and MAPK pathways are commonly drugged pathways in oncology and poised for continued growth given the flurry of innovation and early-stage investment



- The mitogen-activated protein kinase (MAPK) pathway is one of the most perturbed signaling pathways in human cancers; flowing from RAS to RAF to MEK to ERK, the pathway is a master regulator of cellular proliferation and survival
- Cell surface receptor tyrosine kinases, such as EGFR, initiate this cascade based on extracellular cues, setting off phosphorylation of adaptor proteins and activation of the MAPK cascade
- Therefore, the duplication/amplification or mutation of key signaling domains in proteins is a common hallmark of cancer:
  - For example, activating kinase-domain mutations, amplification, overexpression or aberrant localization of EGFR is commonly found in non-small cell lung cancer (NSCLC), colorectal cancer (CRC), glioblastoma (GBM), and head and neck cancers
  - Mutations in BRAF and KRAS are commonly found in melanoma and NSCLC tumors, respectively, and have long been an active area of drug development
- Given the importance of these targets, approved drugs within the space have posted impressive revenue:
  - Launched in 2015, the EGFR tyrosine kinase inhibitor (TKI) Tagrisso (osimertinib) has established itself as a mainstay of therapy in NSCLC, garnering AstraZeneca over $6B in revenue in 2024
  - More recently, targeted agents for specific KRAS mutations Krazati (adagrasib, BMS) and Lumakras (sotorasib, Amgen) have captured approval in NSCLC and CRC, each expecting to clear $500M in annual sales by 2030
- Nevertheless, there is still room for therapeutic improvement: from addressing resistance mutations that arise to current therapies, to developing drugs targeting specific mutations driving oncogenesis, to therapies that may cover more than one mutation in a given signaling node
- Herein, we cover the commercial and development landscape across these paths focusing on small molecule chemistry, look at the transactional space within targeted oncology, and assess the early-stage investment landscape for novel chemistry platforms

Sources: EvalutePharma, Degirmenci U, Wang M, Hu J. cancer therapy. *Cells.* 2020;9(1):198.; *Braicu C et al, Cancers* 2019, *11*(10), 1618; Shi K, et al. *J Hematol Oncol.* 2022;15:94

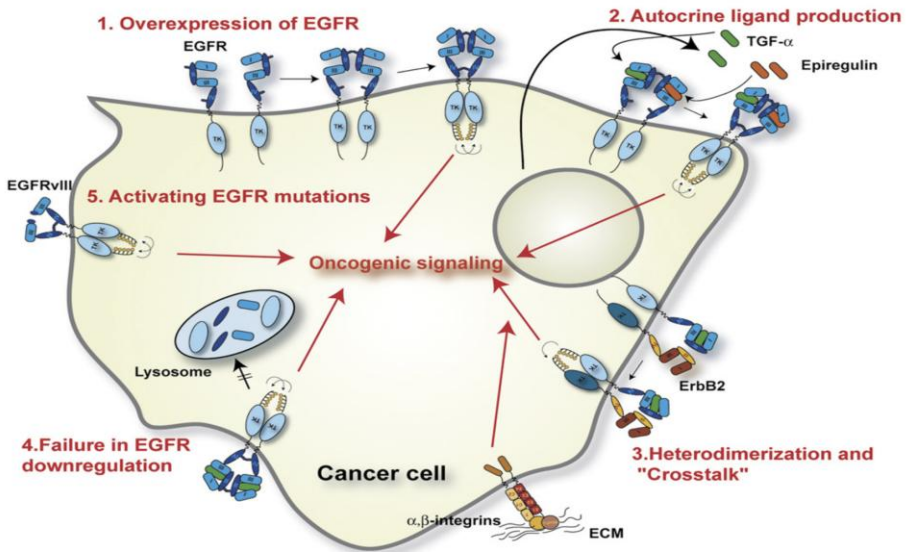
EGFR

EGFR-Driven Oncogenesis and Mutation Spectrum Across Tumor Types

The evolving EGFR mutation spectrum continues to shape biomarker-driven oncology pipelines and clinical development priorities.

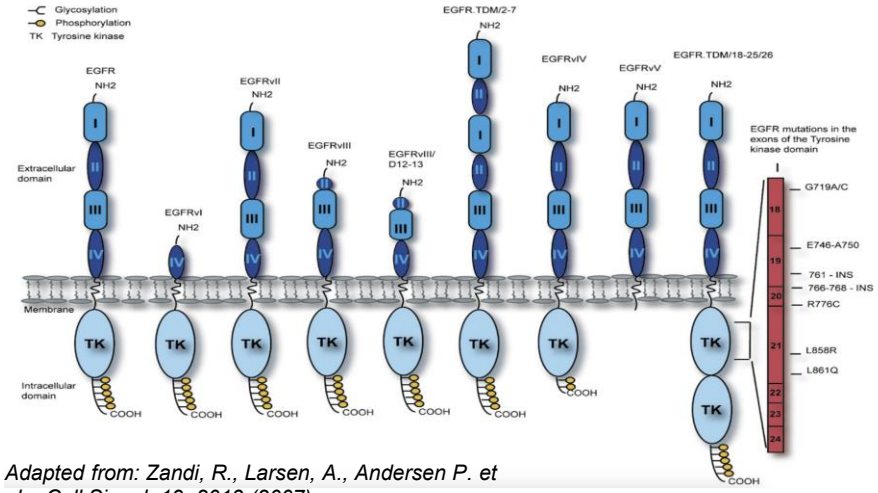
EGFR in Oncogenesis & Tumor Types

- EGFR (ErbB-1) is a receptor tyrosine kinase that drives oncogenesis when aberrantly activated through gene mutation/deletion/overexpression.
- **EGFR alterations are prevalent in epithelial-derived carcinomas:**
  - Non-small cell lung cancer (NSCLC; 10–30%) – exon 19 deletions, L858R mutation
  - Glioblastoma (~50%) – EGFR amplification/EGFRvIII expression.
  - Head & Neck SCC (80–100%) – EGFR overexpression.



Adapted from: Zandi, R., Larsen, A., Andersen P. et al. Cell Signal. 19, 2013 (2007)

EGFR Mutation Landscape



Adapted from: Zandi, R., Larsen, A., Andersen P. et al. . Cell Signal. 19, 2013 (2007)

EGFR mutations occur in both the extracellular and kinase domains.

Extracellular alterations include deletions such as **EGFRvIII (Δ2–7, Δ12–13)**, while key kinase-domain mutations map to specific exons: **exon 18 (G719C), exon 19 (E746_A750 deletions), exon 20 (T790M, insertions)**, and **exon 21 (L858R, L861Q)**. Black symbols indicate glycosylation sites, yellow symbols phosphorylation sites, and blue ovals the tyrosine kinase domain.

EGFR Oncogenic Mechanisms: Oncogenic EGFR activity arises through multiple mechanisms: **(1) overexpression** leading to ligand-independent activation; **(2) autocrine or paracrine ligand production** (*e.g.,* EGF, TGF-α) that reinforces signaling loops; **(3) heterodimerization** with ErbB family receptors (HER2, HER3) amplifying downstream pathways; **(4) defective receptor downregulation** due to impaired ubiquitination or endocytosis, sustaining surface signaling; and **(5) activating kinase-domain mutations** such as exon 19 deletions, L858R, and exon 20 insertions, which drive ligand-independent constitutive activity.

Sources: Zandi et al (2007) Cellular Signalling 19:2013– 2023 (doi:10.1016/j.cellsig.2007.06.023)

Generational Advances in EGFR Tyrosine Kinase Inhibitors (TKIs)

From first- to third-generation EGFR therapies, advances aim to overcome resistance mutations, treatment of central nervous system (CNS) metastases and the pursuit of more durable efficacy

Drug/Generation	Company	Year approved (US)	WW Sales[1]
Gefitinib (Iressa)1st	AstraZeneca	2002	Off Patent
Erlotinib (Tarceva) 1st	Roche	2004	Off Patent
Afatinib (Gilotrif) 2nd	Boehringer Ingelheim	2013	Not Reported
Dacomitinib (Vizimpro) 2nd	Pfizer	2018	Not Reported
Osimertinib (Tagrisso) 3rd	AstraZeneca	2015	$6.5B (2024)
Lazertinib (Lazcluze) 3rd	J&J	2024	$1.2B (e2030)
Sunvozertinib (Zegfrovy) 3rd	Dizal	2025	No estimates
Aurmonertinib (Ameile) 3rd	HANSOH PHARMA	Approved in China	Not Reported

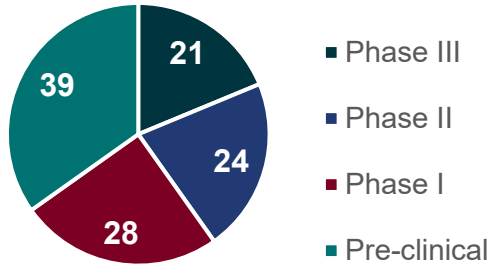
First Generation: TKIs such as gefitinib and erlotinib established EGFR as a validated target in NSCLC, but resistance commonly developed through the T790M mutation (~50–60% of acquired cases)

Second Generation: Irreversible pan-HER inhibitors (afatinib, dacomitinib) were designed to overcome T790M-mediated resistance, yet their clinical use was limited by toxicity (notably rash and diarrhea)

Third Generation: Mutant-selective TKIs like osimertinib provided activity against T790M, with enhanced CNS penetration and fewer off-target effects.

- Approved in 2015 for T790M-positive patients after prior therapy and later as first-line treatment, osimertinib showed superior progression-free survival (PFS) and overall survival (OS)
- FDA-approved (Aug 2024) in combination with amivantamab (Rybrevant), Lazcluze is a reversible third-generation CNS penetrant EGFR TKI used for 1L locally advanced/metastatic EGFR ex19del / L858R
- Sunvozertinib became the first oral exon-20 inhibitor to win US approval (July 2 2025)- accelerated approval covers post-platinum EGFR ex20ins NSCLC

EGFR-Driven Small Molecule Assets by Development Stage[1]



- Small molecules also remain the backbone of targeted therapies such as EGFR inhibitors, constituting 83 out of 112 preclinical – Phase III programs
- Over 70 small molecule programs are in the clinic, spanning novel chemistries/approaches as well as me-too approaches in late-stage development for regional markets

Sources: Company press releases and disclosures; 1) Evaluate Pharma , Westover et al. (2018). Ann Oncol. 15: i10–i19; Landi & Cappuzzo (2013) Transl Lung Cancer Res. 2:202–208; Migliorino et al. (2014). J Clin Oncol. 32; Greig (2016). Drugs 76:263-73

EGFR Pipeline

Fourth-gen products aim to improve potency, CNS penetration, and tolerability; emerging inhibitors aim to tackle resistance mechanisms and redefine standards in EGFR-mutant NSCLC

Asset/ Developer	Mechanism of Action	Status	Estimated Launch Date[1]	Est 2032 Sales (USDm)[1]
Firmonertinib ARRIVENT	TKI for non-classical EGFR mutations (incl. exon 20 insertions)	• Currently completing the Ph3 FURVENT trial in 1L EGFR exon20 insertion NSCLC topline data expected in 2026; with the ALPACCA trial in other NSCLC mutations expected in 2027+ • Approved in China via partner Allist for 1L EGFR mutated NSCLC	2026/7	792M
Zipalertinib cullinan ONCOLOGY TAIHO ONCOLOGY	A mutant-selective EGFR TKI optimized for exon-20 insertions	• REZILIENT1 (NCT04036682) – Phase 1/2 in pretreated EGFR ex20ins NSCLC; Phase 2b met primary ORR endpoint • REZILIENT2 (NCT05967689) – Ongoing Phase 2 study in ex20ins and other uncommon EGFR mutations (including cohorts for 1L, post-ex20ins therapy, uncommon non-ex20ins, and CNS mets)	2026	432
Silevertinib BDTX-15 BLACK DIAMOND THERAPEUTICS	Inhibitor for classical and C797S mutations with robust CNS penetration	• Ongoing Phase 1/2 (NCT05256290; BDTX-1535-101) in: NSCLC with non-classical or acquired-resistance EGFR mutations (including C797S) as well as Glioblastoma (GBM) with EGFR alterations • Silevertinib showed a 60% ORR and an 86% CNS response rate in 43 patients, with no new safety signals observed to date	2027	416
Enozertinib ORIC	TKI targeting EGFR non-classical mutations w/ CNS penetration	• Preliminary data in a Phase 1b in advanced NSCLC patients with EGFR exon20 insertion or EGFR PACC mutations (P-loop and alpha C-helix compressing mutations) showed a 100% CNS response rate (John et al. ESMO Asia (2025), Hong et al. ESMO Asia (2025)) • Additional 1L combination approaches in exon20 EGFR being explored in Phase 1 trials	2027	213
CFT-8919 C4 Therapeutics	Oral protein degrader targeting the L858R EGFR mutation	• Preclinical models show activity against key resistant clones (L858R-C797S, -T790M, -T790M-C797S), offering a resistance-agnostic, TKI-independent MOA • Ongoing study in China in EGFR mutated NSCLC	2029	497

Sources: Company press releases; 1) Evaluate Pharma; Eno et al. (2022) J. Med. Chem, 65: 9662−9677; Low et al. (2023) Ther Adv Med Oncol V15: 1 –19

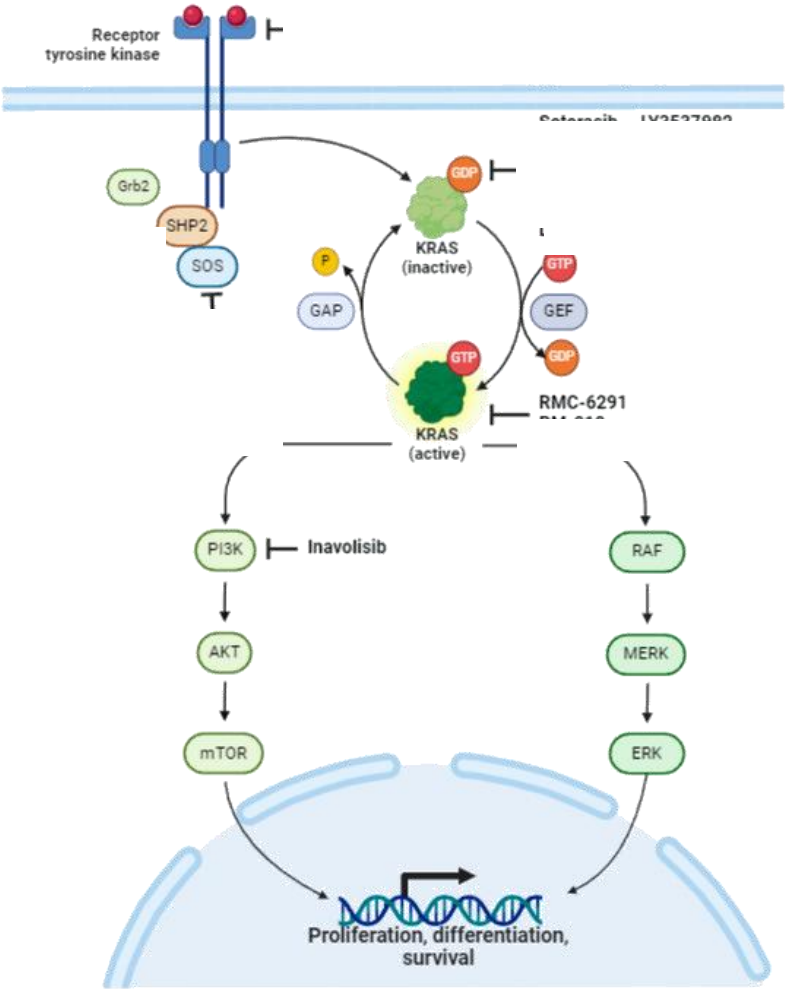
KRAS

KRAS Overview

KRAS mutations are highly prevalent across multiple cancers, particularly NSCLC, colorectal cancer, and pancreatic cancer, as a result, it is the most commonly targeted RAS isoform

- RAS proteins are a family of proteins encoded by three isoforms, HRAS, NRAS, and KRAS, which mediate signals of cell growth and division, sitting at the interface between receptor tyrosine kinases and downstream effectors
- The proteins carry out their function as dictated by their GTP (Guanosine Triphosphate) or GDP (Guanosine Diphosphate) bound state
- When bound to GTP, these molecules are in the “ON” position and subsequently bind and activate downstream signaling molecules such as RAF kinases
- KRAS mutations drive oncogenesis by promoting unchecked growth, blocking apoptosis, and enhancing metastasis
  - Mutations, most often at codons 12, 13, and 61, block its GTPase function and lock KRAS in an active state, driving continuous signaling and uncontrolled proliferation[1]
  - Their high prevalence and central role make KRAS both a key biomarker and an important therapeutic target
- The oncogenic potential of KRAS is well established across several tumor types:
  - Pancreatic ductal adenocarcinoma (PDAC): >90% of cases harbor KRAS mutations, making it the defining driver event in this disease
  - Colorectal cancer (CRC): ~40% of tumors carry KRAS mutations
  - NSCLC: ~25–30% of adenocarcinomas exhibit KRAS alterations, with KRAS G12C as the most common variant[2].

Cancer Type	KRAS	G12C	G12D	G12V	G12X	G13X	Q61X
NSCLC	23%	41%	12%	22%	88%	5%	2%
Esophageal	4–9%	6%	25%	19%	53%	19%	<1%
Cholangiocarcinoma	9–18%	5%	35%	22%	71%	5%	13%
Pancreatic	91%	1%	39%	31%	91%	2%	7%
Colorectal	30–44%	7%	28%	20%	65%	19%	5%



Adapted from: Ros J et al Int. J. Mol. Sci. 2024, 25(6), 3304

Sources: 1) Huang et al. (2021) Signal Transduction and Targeted Therapy. 6:386; 2) Parikh et al. (2022) Journal of Hematology & Oncology 15:152

Next-Generation and Novel KRAS Agents

Next-generation KRAS G12C & D inhibitors aim to overcome resistance and extend clinical benefit

Evolution of KRAS G12C Inhibitor Generations

- **First-generation KRAS-G12C inhibitors** (sotorasib, adagrasib) were the first covalent agents to irreversibly target the inactive GDP-bound state of KRAS, establishing proof-of-concept for drugging KRAS and achieving regulatory approvals in NSCLC and CRC[1]
- **Second-generation KRAS-G12C inhibitors** (olomorasib, divarasib, MK-1084, JDQ443) were designed to overcome the limitations of first-generation agents by improving potency, selectivity, and pharmacokinetics. They aim to achieve more durable responses and broader activity across tumor types, with most currently in mid-stage clinical trials
- **Third-generation KRAS-G12C inhibitors** are in preclinical and early clinical stages, designed to overcome resistance mechanisms such as nucleotide exchange and adaptive feedback loops
  - They are expected to deliver stronger binding, broader activity in resistant tumors, and improved pharmacological profiles; emerging candidates include optimized derivatives (*e.g.,* ARS1620 and ON-state inhibitors like RMC-6291)[2]
- In addition to G12C, KRAS G12D inhibitors have progressed from first-generation agents like MRTX1133, which delivered strong preclinical regression but faced PK and delivery limitations, to second-generation compounds designed for better durability, broader tumor coverage, and improved pharmacokinetics[3]
- Third-generation and emerging approaches—including degraders, multi-state inhibitors, and novel scaffolds—aim to overcome resistance and bypass pathways, with multiple programs advancing through preclinical development[3]

Asset	Company	Indications	Est 2030 Sales (USDm)[3]
Krazati (Adagrasib)	Bristol Myers Squibb	Colorectal cancer, NSCLC	596
Lumakras (sotorasib)	AMGEN	NSCLC, Colorectal cancer	573

Evolution of KRAS G12C Inhibitors

1 **First Generation** (e.g., Sotorasib, Adagrasib)
- First selective covalent inhibitors
- Limitation: resistance, PK issues

2 **Second Generation** (e.g., Divarasib, Olomorasib)
- Improved potency & PK/PD
- Ongoing NSCLC & CRC trials
- Aim: longer, broader responses

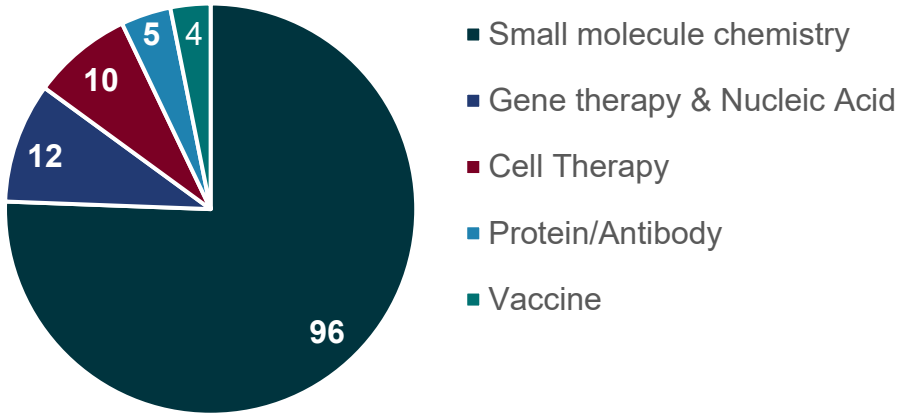
3 **Third Generation** (emerging)
- To overcome resistance
- Better binding and PK
- Preclinical/early clinical stage

Sources: 1) Nokin et al. (2024) Nature Communications. 15:7554; 2) Isermann et al. (2025) Trends in Cancer. 1:91-116; 3) Evaluate Pharma

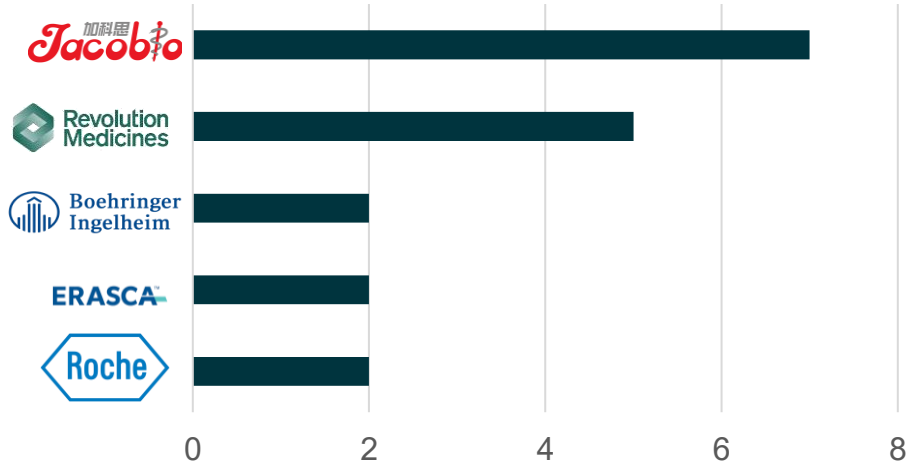
KRAS Pipeline

Early stage pipeline highlights significant opportunity, with multiple players advancing competitive portfolios across oncology

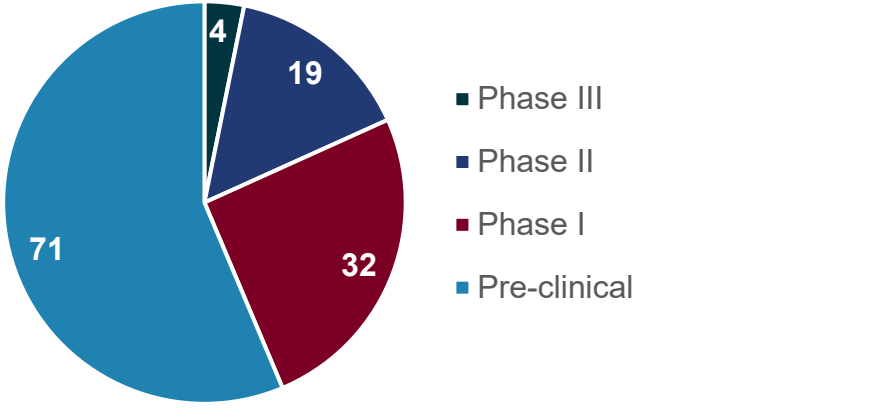
Technology Distribution in the KRAS Therapeutics Pipeline



Companies with multiple assets in development (pre-clinical to PIII)



KRAS-targeted Assets by Development stage



- Small molecules account for the majority of assets in preclinical and clinical development within the KRAS space
- Large pharma such as BI and Roche as well as emerging players such as Jacobio, Revolution, and Erasca are devoting resources to more than one pre-commercial asset in development
- As compared to the EGFR pipeline, there are a larger variety of novel modalities attempting to drug RAS, such as cell therapies
- Many of these companies are developing engineered T cells which seek out and eliminate cancer cells harboring immunogenic KRAS epitopes (e.g., Affini-T & Anocca)

Sources: Evaluate Pharma, company disclosures and press releases

Next-Generation KRAS G12C

There are a variety of late-stage G12C programs, the majority of which are in development for NSCLC

Asset/Sponsor	RAS Target	Phase	Comments
Olomorasib Lilly	KRAS G12C	**3**	• A Phase 3 trial (NCT06119581) is ongoing to compare first-line treatment with Olomorasib + Pembrolizumab (with or without chemotherapy) versus placebo + pembrolizumab in KRAS G12C-mutant NSCLC • A Phase 1/2 study (NCT04956640) is evaluating olomorasib (with or without pembrolizumab and/or cetuximab) in various KRAS G12C-mutant solid tumors • The FDA granted Breakthrough Therapy Designation (Sept 2025) to olomorasib plus pembrolizumab for first-line treatment of unresectable advanced/metastatic KRAS G12C-mutant NSCLC with PD-L1 ≥ 50%[1] • Olomorasib combined with pembrolizumab demonstrated an ORR of 73.9% in KRAS G12C-mutant NSCLC in a Phase 1/2 trial (NCT04956640)[2]
Divarasib (aka GDC-6036) Roche Genentech A Member of the Roche Group	KRAS G12C	**3**	• A Phase 3 trial (NCT06497556) is underway to compare Divarasib versus the current standard-of-care KRAS G12C inhibitors (e.g., Sotorasib or Adagrasib) in NSCLC • Data released to date: In a Phase 1 dose-escalation/expansion study single-agent Divarasib achieved confirmed response of 53.4% in NSCLC patients and 29.1% in CRC patients[3] • In a subsequent Phase 1b combination cohort of KRAS G12C-mutant colorectal cancer patients treated with Divarasib plus Cetuximab, the ORR was 62.5%[4]
MK-1084 MERCK	KRAS G12C	**3**	• Phase 3 studies are planned: KANDLELIT-012 (MK-1084 + cetuximab/mFOLFOX6 in 1L KRAS G12C CRC-NCT06997497) and KANDLELIT-004 (MK-1084 + KEYTRUDA 1L KRAS G12C NSCLC NCT06345729) • Data released to date: Early studies have shown 38-46% ORR in heavily pretreated KRAS G12C patients (monotherapy and anti-EGFR mAb cetuximab) and early activity in 1L mCRC mFOLFOX6 with AE profiles consistent with EGFR and chemo combos[5]

Sources: 1) Eli Lilly and Company. BioSpace, 4 Sept 2025.; 2) Burns T. et al. J Thorac Oncol. 2025 (In press).; 3) Sacher A. et al. N Engl J Med. 2023;389(8):710-721.; 4)Alonso D. et al. Nature Medicine. 2024;30:271–278.; 5) Lugowska I. et al. J Clin Oncol. 2025;43(suppl 17):3508

Next-Generation KRAS G12C

NSCLC data to date for next-gen G12C assets compare favorably to established commercial molecules (1 of 2)

Monotherapy Data	Adagrasib[1]	Sotorasib[2]	Olomorasib[3,4]	Divarasib[5]	MK-1084[6]
Study	KRYSTAL-1 (NCT03785249)	CodeBreaK 100 (NCT03600883)	LOXO-RAS-20001(mono update) (NCT04956640)	GO42144 (NCT04449874) (divarasib mono)	KANDLELIT-001 (NCT05067283) (mono cohort)
Phase	1/2 (registrational phase 2 cohort)	1/2	1/2	1	1
Design	Open-label, single-arm	Single-arm; ORR by independent central review	Open-label dose escalation/expansion	Open-label dose escalation/expansion	Open-label
Regimen	600 mg PO BID	Sotorasib 960 mg PO QD	monotherapy	400 mg PO QD cohort highlighted	monotherapy
Patient population	KRAS G12C advanced/metastatic NSCLC; previously treated; N=116 treated / n=112 measurable	KRAS G12C advanced NSCLC; previously treated	KRAS G12C advanced NSCLC; includes KRAS G12Ci-naïve and prior KRAS G12Ci cohorts	KRAS G12C NSCLC (400 mg cohort N=44 reported)	Previously treated KRAS G12C metastatic NSCLC; N=21 (reported)
ORR	42.9%	37.1%	43% (G12Ci-naïve) and 41% (prior G12Ci)	59.1% (400 mg NSCLC cohort)	38% (95% CI 18–62)
PFS	mPFS 6.5 mo	mPFS 6.8 mo	mPFS 8.1 mo (both G12Ci-naïve and prior G12Ci cohorts reported)	mPFS 15.3 mo (400 mg NSCLC cohort)	NR
DOR	mDOR 8.5 mo	mDOR 11.1 mo	NR	mDOR 14.0 mo (400 mg NSCLC cohort)	NR
Safety (TRAEs)	Any-grade 97.4%; grade ≥3 44.8%	Any-grade 69.8%; grade 3 19.8%; grade 4 0.8%	TRAE-related discontinuation 1% (additional TRAE detail not in release)	(Overall safety set, all tumors) any-grade TRAEs 93%; grade 3–5 11%; withdrawal 2%	(Monotherapy arm-level) TRAEs 58% (grade breakdown not provided in release)

Sources: 1) ASCO. 2 Jun 2022.; 2) N Engl J Med. 24 Jun 2021.; 3) ASCO. 12 August 2024.; 4) Lilly. News Release. 1 June 2024.; 5) ASCO. October 2025.; 6) ASCO. June 2025/

Next-Generation KRAS G12C

NSCLC data to date for next-gen G12C assets compare favorably to established commercial molecules (2 of 2)

1L Combination	Adagrasib[1]	Sotorasib[2]	Olomorasib[3]	MK-1084[4]
Study	KRYSTAL-7 (NCT04613596)	CodeBreaK 101 (NCT04185883)	LOXO-RAS-20001 (NCT04956640) (olomorasib+pembro)	KANDLELIT-001 (NCT05067283)
Phase	2	1B	1/2	1
Regimen(s) reported	Adagrasib + pembrolizumab	Sotorasib + carboplatin/pemetrexed (then maintenance sotorasib+pemetrexed)	Olomorasib (50–100 mg BID) + pembrolizumab	MK-1084 + pembrolizumab and MK-1084 + pembrolizumab + chemo (carbo/pem)
Patient population	1L KRAS G12C mNSCLC, PD-L1 TPS ≥50% cohort summarized	1L KRAS G12C advanced NSCLC subgroup	Report includes a first-line subgroup; paper reports (first-line) ORR + safety across treated set	Untreated metastatic NSCLC cohorts reported; PD-L1 TPS ≥1% for MK-1084+pembro cohort; N's disclosed
ORR	59.3%	65%	73.9% (first-line subgroup)	77% (MK-1084+pembro; N=69) and 53% (MK-1084+pembro+chemo; N=40)
mPFS	27.7 mo	mPFS 10.8 mo (article also notes PD-L1 negative mPFS 11.9 mo)	NR (not reported in abstract excerpt)	NR
DOR	NR	NR	NR	NR
Safety (TRAEs)	Any-grade TRAEs 95% (trial page summary; grade breakdown NR there)	Article reports TRAEs 49% in the 1L group (grade breakdown NR in the article)	Any-grade TRAEs 81.7%; grade ≥3 33.3%; discontinuation of both therapies 6.5%	TRAEs 94% (MK-1084+pembro) and 93% (MK-1084+pembro+chemo) (grade breakdown NR in release)

Sources: 1) ASCO. June 2025.; 2) ASCO. June 2024.; 3) J Thorac Oncol. 29 NOV 2025.; 4) MERCK. News Release. 30 May 2025

Next-Generation KRAS G12C

Earlier stage G12C assets are targeting the “ON” and/or “OFF” states of the kinase

Asset/Sponsor	RAS Target	Phase	Comments
Fulzerasib (GFH925) GENFLEET THERAPEUTICS	KRAS G12C	**US: Phase 3**	• Approved in China with partner Innovent for adult patients with advanced non-small cell lung cancer (NSCLC) carrying the Kirsten rat sarcoma viral oncogene (KRAS) G12C mutation who have received at least one systemic treatment • GenFleet announced FDA clinical trial approval for a Phase 3 registrational study of GFH925 monotherapy in refractory metastatic CRC (KRAS G12C) (GFH925X0301 trial)
BBO-8520 BBOT BridgeBio Oncology Therapeutics	Direct KRAS G12C	**1a/b**	• Direct KRAS G12C inhibitor (targets both ON and OFF states of KRAS G12C) • Phase 1a/1b clinical trial (ONKORAS-101, NCT06343402), as monotherapy and in combination with pembrolizumab in KRAS G12C mutant NSCLC • Data released to date: BBO-8520 showed a 65% objective response rate and 66% six-month progression-free survival, alongside a generally manageable safety profile[1]
Elironrasib (RMC-6291) Revolution Medicines	KRAS G12C	**1**	• Elironrasib targets the active, GTP-bound “On form” of KRAS G12C[6] • Ongoing Phase 1 monotherapy & combination trials (NCT06128551, NCT05462717, NCT06162221) in patients with advanced KRAS G12C-mutated solid tumours, including NSCLC in patients previously treated with a KRAS G12C inhibitor • FDA granted Breakthrough Therapy Designation in locally advanced (LA) or metastatic KRAS G12C-mutated NSCLC with prior chemotherapy and immunotherapy but no prior KRAS G12C inhibitor[2] • Data released to date: In a Phase 1 trial of Elironrasib in 24 patients with metastatic NSCLC harboring KRAS G12C, 42% of patients achieved a partial response[3]

Sources: 1) Company press release, Jan 7, 2026.; 2) Revolution Medicines. News release, Jul 23, 2025.; 3) American Association for Cancer Research (AACR). News release, 22 October 2025

KRAS G12D Inhibitors (Clinical Stage)

With G12C validated as a high-value clinical and commercial target, there is significant interest in drugging the G12D mutation (1 of 2)

Asset/Sponsor	RAS Target	Phase	Comments
Zoldonrasib (RMC-9805) Revolution Medicines	KRAS G12D	**1b/2**	• Similar to Elironrasib, Zoldonrasib targets the active, GTP-bound "On form" of KRAS G12D[1] • A Phase 1, multicenter, open-label study (NCT06040541) is enrolling adults with advanced solid tumors harboring KRAS G12D mutations to evaluate the safety and clinical activity of RMC-9805 • Data released to date: In a dose-escalation/dose-expansion Phase 1 trial, zoldonrasib achieved a 61% ORR in evaluable patients with KRAS G12D-mutant NSCLC and a 30% ORR in KRAS G12D-mutant PDAC[2]
VS-7375/GF-375 GENFLEET THERAPEUTICS VERASTEM ONCOLOGY	KRAS G12D	**1/2a**	• Binds both GDP- and GTP-bound states "OFF and ON"[3]; Chinese rights owned by GenFleet Phase 1/2 (NCT07020221) trial initiating in previously treated PDAC patients with KRAS mutations • Granted Fast Track Designation for patients with advanced or metastatic KRAS G12D PDAC[4] • Data released to date: Early data presented at ESMO 2025 from a China-based study of GFH375 in PDAC showed an ORR of 41%[5]
INCB161734 Incyte	KRAS G12D	**1**	• A non-covalent approach that binds GDP & GTP bound forms[6] • A Phase 1 (NCT06179160) is enrolling with metastatic solid tumors including PDAC, CRC, and NSCLC • Data released to date: Presented data at ESMO 2025, in advanced PDAC KRAS G12D-mutant showing ORRs 20-34% across dosing cohorts[7]
HRS-4642 HENGRUI	KRAS G12D	**1**	• A non-covalent KRAS G12D inhibitor[8] being evaluated in a Phase 1 dose-escalation and dose-expansion study (NCT06385678) in patients NSCLC and PDAC patients who harbor the KRAS G12D mutation[8] • Data released to date: In a Phase 1 monotherapy study, HRS-4642 showed ORRs of 21–33% in patients with KRAS G12D-mutant PDAC and NSCLC[8].
QTX3034 Quanta THERAPEUTICS INC.	G12D-biased multi-KRAS	**1**	• A Phase 1 trial (NCT06227377) is enrolling patients with advanced solid tumors harboring KRAS G12D mutations, is testing monotherapy and combination therapy (Cetuximab), including CRC, PDAC, and endometrial cancer • FDA cleared the investigational new drug (IND) application for QTX3034 in June 2024[9] • Data released to date: QTX3034-cetuximab combination achieved significant anti-tumor activity in patients with refractory CRC and PDAC (2025 AACR-NCI-EORTC)[10]
ASP3082 astellas	KRAS G12D Degrader	**1**	• A PROTAC recruiting KRAS G12D to cellular degradation machinery[11] which is currently being evaluated in a dose-escalation study (NCT05382559) in NSCLC, CRC, PDAC +/- cetuximab • Data released to date: In presentations at ESMO 2024, early-phase data showed acceptable safety, with only ~5% of patients experiencing grade ≥3 TRAEs and, at 300 mg dose, a 33 % ORR in patients with NSCLC[12]

Sources: Company press releases and disclosures 1) Arbour K. et al. Cancer Res. 2025; 85 (8_Suppl_3):CT019.; 2) Arbour KC, et al. AACR, 2025; Abstract # CT019 3) Pachter J. et al. Cancer Res. 2025; 85 (8_Suppl_1):4394.; 4) DiEugenio J. OncLive, July 25, 2025.; 5) Zhou A, et al. ESMO Congress 2025.; 6) Farren M. et al. Cancer Res. 2024; 84(6_Supplement): 5900.7) Desai J. et al. ESMO Congress 2025; October 17–21, 2025.; 8) Xiong A. ESMO Congress 2025 (Abstract 915O).; 9) Quanta Therapeutics. (2024, January 4).; 10) Quanta Therapeutics. Press release, 24 October 2025.; 11) Oya Y. et al. Lung Cancer. 2024;194:107886.; 12) Park W, et al. Annals of Oncology. 2024;35(Suppl_2):S486–S487

KRAS G12D Inhibitors (Clinical Stage)

With G12C validated as a high-value clinical and commercial target, there is significant interest in drugging the G12D mutation (2 of 2)

Asset/Sponsor	RAS Target	Phase	Comments
TSN1611 Tyligand Bioscience	KRAS G12D	1/2	• TSN1611 is a highly selective KRAS G12D inhibitor that engages both the active (GTP-bound) and inactive (GDP-bound) forms of the mutant protein[1] • An ongoing first-in-human, open-label, multi-center Phase 1/2 study is being conducted in advanced solid tumors, with primary completion expected in October 2026 (NCT06385925)
QLC1101 齐鲁制药 OILU PHARMACEUTICAL	KRAS G12D	1	• A reversible non-covalent inhibitor KRAS G12D mutation binding,[2] currently in an ongoing Phase 1 clinical trial in patients with advanced solid tumors (NCT06403735), with the monotherapy arm expected to reach primary completion in May 2026 • A separate Phase 1b/2 combination study (NCT06949761) is planned but not yet recruiting, with a primary completion date listed as April 2027
QTX3046 Quanta THERAPEUTICS INC	KRAS G12D	1	• An orally bioavailable allosteric inhibitor of the oncogenic KRAS G12D mutation which inhibits both the GDP-bound and GTP-bound (OFF/ON) conformations[3] • A Phase 1 clinical trial in patients with advanced solid tumors is evaluating the drug both as monotherapy and in combination with cetuximab (an EGFR inhibitor), with primary completion expected in July 2027 (NCT06428500)
LY3962673 Lilly	KRAS G12D	1a/1b	• A selective, oral, non-covalent KRAS G12D inhibitor[4] currently in a Phase 1a/1b clinical trial assessing mono- and combo- therapy arms in KRAS G12Dmutant advanced solid tumors, with primary completion expected in March 2029 (NCT06586515)

Sources: Company press releases and websites, 1) Shang E. et al. Cancer Research. 2024; 84(6_Supplement): 3315.; 2) Tang D, et al. BMJ Oncology. 2025; 4(1):e000946.; 3) Vo E. et al. Cancer Research. 2023; 83 (8_Supplement): LB321.; 4) Gong X. et al. Cancer Research. 2024;84 (6_Supplement):3316

Multi-KRAS Inhibitors (Clinical Stage)

In addition to specific mutations, a number of companies are developing assets to drug multiple KRAS mutations (1 of 2)

Asset/Sponsor	RAS Target	Phase	Comments
BI 3706674 Boehringer Ingelheim	Multi KRAS	1	• BI 3706674 inhibits multiple KRAS variant alleles, including mutants such as G12V, as well as wild-type KRAS in the GDP-bound (inactive/OFF) state[1] • A Phase 1 clinical trial in adults with advanced solid tumors, including gastric, oesophageal, and gastro-oesophageal junction adenocarcinoma with KRAS wild-type amplification or KRAS mutations, is ongoing with primary completion expected in December 2025 (NCT06056024)
BGB-53038 BeiGene	Pan-KRAS	1	• Targets mutated KRAS or amplified KRAS proteins and is being tested in an ongoing Phase 1 clinical in patients with advanced solid tumors harboring KRAS mutations, with primary completion expected in December 2026 (NCT06585488)
PF-07934040 Pfizer	Pan-KRAS	1	• An oral inhibitor of KRAS-dependent signaling in a Phase 1 clinical trial in KRAS mutated tumors including NSCLC, PDAC and CRC with primary completion expected in September 2027 (NCT06447662)
JAB-23E73 AstraZeneca	Pan KRAS	1/2a	• JAB-23E73 is an orally bioavailable pan-KRAS inhibitor that targets both the active and inactive forms of mutated or amplified KRAS in advanced solid tumors[2] • A multicenter, open-label Phase 1/2a study is assessing JAB-23E73 in adult patients with advanced solid tumors harboring KRAS gene alterations (mutations or amplifications), with primary completion expected in November 2027 (NCT06973564)

Sources: Company press releases and disclosures; 1) Tedeschi A, et al. Cancer Research. 2024;84(6_Supplement):3317; 2) Wang P. et al. Molecular Cancer Therapeutics. 2025; 24(10_Supplement): A068

Multi-KRAS Inhibitors (Clinical Stage)

In addition to specific mutations, a number of companies are developing assets to drug multiple KRAS mutations (2 of 2)

Asset/Sponsor	RAS Target	Phase	Comments
ALTA3263 Alterome THERAPEUTICS	Pan KRAS	1	• The compound inhibits both “ON” (GTP-bound, active) and “OFF” (GDP-bound, inactive) KRAS • A multicenter, open-label Phase 1/1b study is enrolling adult patients with advanced solid tumors harboring KRAS mutations (NSCLC, CRC, PDAC) — with primary completion expected in May 2029 (NCT06835569)
LY4066434 Lilly A MEDICINE COMPANY	Pan KRAS	1	• An inhibitor of a broad range of KRAS variants (i.e., G12D, G12V, G12C, G13D, G12A, and G12S), and wild-type KRAS, while sparing HRAS and NRAS[1] • A multicenter, open-label Phase 1a/1b study is testing the pan-KRAS inhibitor in adults with advanced solid tumors harboring KRAS mutations, with primary completion expected in January 2030 (NCT06607185).
ERAS-4001 ERASCA™	Pan KRAS	1	• Inhibitor designed to address multiple KRAS mutations as well as wild-type KRAS activation • Currently recruiting the BOREALIS-1 study assessing safety and tolerability in advanced or metastatic solid tumors with certain KRAS mutations (NCT07021898)
BBO-11818 BBOT BridgeBio Oncology Therapeutics	Pan KRAS	1	• Oral, non-covalent pan-KRAS inhibitor that binds KRAS in both “ON” (GTP-bound) and “OFF” (GDP-bound) states • Phase 1 trial recruiting in adult subjects with KRAS mutations with multiple therapeutic combinations (e.g., pembrolizumab, cetuximab, etc.) (NCT06917079)
AMG-410 AMGEN	Pan KRAS	1	• Oral pan-KRAS inhibitor designed to inhibit multiple KRAS alterations while sparing NRAS/HRAS • Enrolling Phase 1/1b study of AMG-410 alone or in combination in patients harboring KRAS mutations (NCT07094113)

Sources: Company press releases and disclosures; 1) Gao H et al. Cancer Research. 2025; 85(8_Supplement_1): 4375

Multi RAS Inhibitors (Clinical Stage)

Further, there is keen interest in developing approaches to drug not only KRAS mutations, but approaches to target multiple RAS isoforms with one molecule

Asset/Sponsor	RAS Target	Phase	Comments
Daraxonrasib (RMC-6236) Revolution Medicines	Multi RAS	3	• It is an orally-available, non-covalent, tri-complex inhibitor that targets the active (GTP-bound) form of multiple RAS isoforms • Daraxonrasib is being studied in a Phase 3 trial in adult patients with previously treated metastatic PDAC and NSCLC, with a primary completion date of July 2026 (NCT06625320). • Data released to date (NCT05379985): Long-term follow-up data for daraxonrasib in second-line metastatic PDAC show a confirmed objective response rate (ORR) of approximately 29% (the broader group of patients with any RAS mutation)–35% (subgroup of patients whose tumors harbored a KRAS G12X mutation)[1]
YL-17231 (TEB-17231) 280BIO	Multi RAS	1	• The compound inhibits RAS signaling (KRAS, NRAS, HRAS) and in preclinical studies showed activity across multiple RAS-mutant tumor cell lines (including KRAS G12C, G12D, and G12V)[2] • A Phase 1, multicenter, open-label study is testing YL-17231 in adults with advanced solid tumors harboring KRAS, HRAS, or NRAS mutations, with primary completion expected in October 2025 (NCT06096974)
ERAS-0015 ERASCA	Multi RAS	1	• ERAS-0015 acts as an oral, pan-RAS molecular glue that binds RAS in its active, GTP-bound state and forms a high-affinity complex that sterically blocks RAS–effector interactions[3] • A Phase 1, multicenter, open-label study is underway in adults with advanced solid tumors harboring RAS mutations to evaluate ERAS-0015; the trial's primary completion is expected in May 2028 (NCT06983743)
RO7673396 Roche	Multi RAS	1	• Currently recruiting a Phase 1 assessing safety and tolerability in advanced or metastatic solid tumors with certain KRAS mutations (NCT06884618)
GF-276 GENFLEET THERAPEUTICS	Multi RAS	1 (China)	• A Pan RAS molecular glue approach currently in Phase 1 development in China

Sources: Company press releases and disclosures; 1) Revolution Medicines. September 10, 2025. 2) Xu Z. et al. Abstract presented at AACR 2023 Annual Meeting; abstract # 2627; 3) Lew E. et al. AACR Annual Meeting 2025. Cancer Research. 2025; 85(8_Supplement_1): 390

BRAF/MEK/ERK

RAF/MEK/ERK – Overview

The mitogen-activated protein kinase (MAPK) cascade is a key regulator of normal cell proliferation, survival, and differentiation, and therefore is commonly dysregulated in many cancers

RAF is a serine/threonine kinase downstream of RAS and upstream of MEK

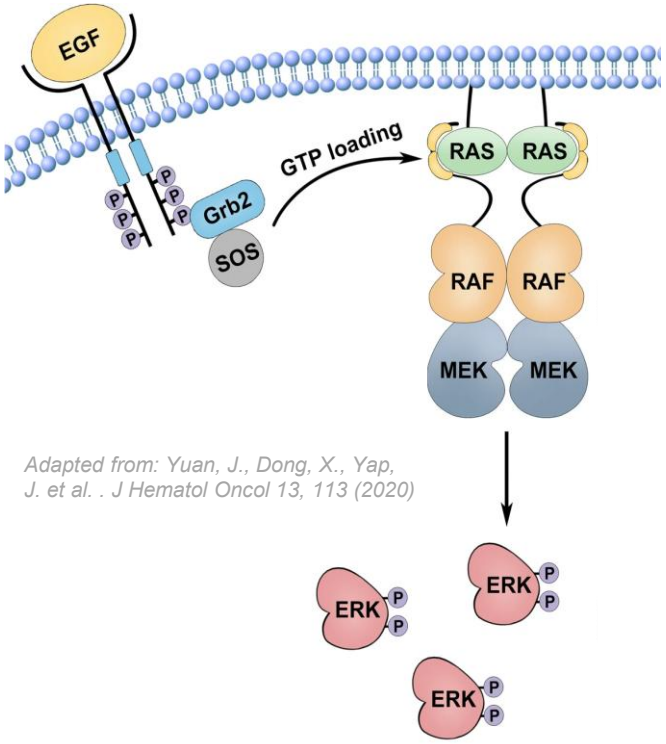
- The common V600E mutation locks BRAF in a constitutively active state, independent of upstream signals, leading to persistent MEK/ERK activation
- BRAF mutations are classified in a number of ways based on mutation type, RAS-dependence, and others
- These alterations are seen in melanoma, colorectal, thyroid, and lung cancers rendering tumour cells “addicted” to MAPK signalling in unchecked growth and apoptosis resistance

MEK1/2 (encoded by MAP2K1/MAP2K2 proteins) are the immediate downstream effectors of RAF and the sole kinases that activate ERK1/2

- Dysregulation occurs either by upstream activation (*e.g.,* mutated BRAF or RAS) or, more rarely, direct MEK activating mutations
- MEK-altered tumors have been reported in melanoma, colorectal cancer, non-small cell lung cancer, and Langerhans cell histiocytosis

ERK1/2 (extracellular signal-regulated kinases) are MAPKs that, upon activation, can regulate 100+ substrates including transcription factors, cytoskeletal regulators, and enzymes — thus influencing proliferation, differentiation, and survival

- In oncogenic settings (e.g., BRAF or RAS mutations), ERK is chronically activated, or its regulation is perturbed, leading to sustained signals for growth
- Direct activating ERK mutations are relatively rare in human cancers (unlike BRAF/RAS) because excessive ERK activity can be deleterious (causing senescence, apoptosis)
- Further, negative-feedback regulators that normally restrain ERK may be impaired or hijacked in tumors



Adapted from: Yuan, J., Dong, X., Yap, J. et al. . J Hematol Oncol 13, 113 (2020)

Tumor type	BRAF mutation	MEK1 mutation
Melanoma	30–70%	7%
Thyroid carcinoma	30–50%	-
Serous ovarian	30%	-
Colorectal	5–20%	2%
Cholangiocarcinoma	20%	2%

Roberts and Dar (2007). Oncogene 26, 3291–3310; Yuan, J., Dong, X., Yap, J. *et al.* The MAPK and AMPK signaling: interplay and implication in targeted cancer therapy. *J Hematol Oncol* **13**, 113 (2020)

MAPK – Approved Drugs

The MAPK signaling cascade remains a cornerstone in tumors such as melanoma, with market leaders commanding strong sales performance and newer entrants launching into niche indications

FDA-Approved RAF and MEK Inhibitors

Drug (Company)	Target	First Approval	WW Sales /Year [1]	Indications
Tafinlar (dabrafenib, Novartis)	BRAF	2013	$2.1B sales reported in combination / 2024	Melanoma NSCLC, ATC
Mekinist (trametinib, Novartis)	MEK1	2013		Melanoma NSCLC, ATC
Braftovi (encorafenib, Pfizer)	RAF	2018	$607M/2024	Melanoma NSCLC, ATC
Mektovi (binimetinib, Pfizer)	MEK	2018	$274M/2024	Melanoma NSCLC, ATC
Zelboraf (vemurafenib, Roche)	RAF	2011	$89M/2024	Melanoma
Cotellic (cobimetinib, Roche)	MEK1	2015	$47M/2024	Melanoma
Gomekli (mirdametinib, SpringWorks, Merck KGaA)	MEK	2025	$1,044M (2032 EST)	Neurofibromatosis type 1-associated plexiform neurofibromas
Ojemda (tovorafenib, DayOne)	RAF	2024	$1,197M (2032 EST)	Pediatric Low-Grade Glioma w/ BRAF alterations

- Legacy MEK/RAF products have largely focused on targeting BRAF-mutated melanoma
- Novartis leads the MAPK-targeted therapy market, generating nearly $3B annually from its combined BRAF and MEK inhibitor portfolio
- Pfizer continues to grow Braftovi sales post-Array BioPharma acquisition, reinforcing the interest in the RAF/MEK pathway
- Despite the historic success, drug-resistant ERK reactivation occurs in up to 40% of RAF/MEK-pretreated tumors, underscoring a major therapeutic gap
- Newer agents have garnered approval for niche patient populations
- In February 2025, the FDA approved Gomekli (mirdametinib) for patients ≥2 years old with NF1 and symptomatic plexiform neurofibromas not amenable to complete resection
- FDA granted accelerated approval in April 2024 to DayOne's Ojemda in patients ≥6 months old with relapsed or refractory pediatric LGG with BRAF fusion, BRAF rearrangement, or BRAF V600 mutation

Sources: 1) Evaluate Pharma; company press releases

ERK1/2 Inhibitors

Oral ERK1/2 inhibitor small molecules, ulixertinib and beroterkib, have both undertaken basket trials in patients with mutations within the MAPK pathway

Asset, Company	Mechanism of Action	Next Readout	Phase	Patient Population	Evidence to Date and Comments
beroterkib astex pharmaceuticals	Dual inhibitor of ERK Phosphorylation and ERK catalytic activity	Completed on 2025-03-03	Phase 1/2 (n=192) (NCT03520075)	Patients with gene aberrations in the MAPK pathway	• **Safety:** It is well tolerated with manageable AEs (nausea, diarrhea, transaminitis, rash, fatigue) • **Efficacy:** Induced PR in four subjects; ORR (CR+PR):12.5%; mOS: 11.2 months; mDoR: 8.5 months[1]
Ulixertinib (BVD-523) BIOMED VALLEY DISCOVERIES	ERK 1 & 2 Inhibitor	Ongoing; estimated end date in Nov 2026	Phase 1 (n=45) NCT03454035	Advanced solid tumor with NRAS mutations (G12, G13, or Q61), or KRAS (G12/G13), or HRAS G12/G13	• More than 400 patients treated to date across multiple studies, with limited clinical data released since 2018. • In combination with Palbociclib. • **Safety:** DLTs included grade 3 fatigue, grade 3 acute kidney injury, and hyponatremia. Common adverse events included fatigue, rash, nausea. • **Efficacy:** Three out of 16 patients achieved SD; mPFS: 2 months[2]

Two companies have recently deprioritized ERK inhibitors:

- LY3214996/temuterkib is no longer listed in Eli Lilly's official public clinical development pipeline, but it continues to be evaluated in ongoing early-phase oncology trials, with Lilly still involved—so it's likely deprioritized rather than fully discontinued
- Erasca's ERAS 007 is active but not currently recruiting advanced gastrointestinal cancers; the company has de-prioritized the asset

1 Raybould et al. (2021) ASCO Annual Meeting
2 Wahlroos et al. (2024) ASCO Annual Meeting

MEK Inhibitors

Multiple RAF proteins are in development across a range of indications, with Verastem's Phase 3 VS-6766 granted breakthrough status in ovarian cancer

Asset, Company	Target	Next Readout	Phase	Patient Population	Clinical Data To Date
Avutometinib VS-6766 VERASTEM ONCOLOGY	RAF/MEK Clamp	Planned filing based on early data, confirmatory readout 2H 2028 NCT06072781: Estimated completed date in 2031-02-09	**Phase 2** (n=57) NCT03875820 **Phase 3** (n=270) NCT06072781	Low-grade serous ovarian cancer (LGSOC) who have progressed after platinum-based therapy.	**Phase 2** • **Safety:** Relatively tolerable • **Efficacy:** ORR in **KRAS-mutant** subset: ORR = 44%; **KRAS wild-type** subset: ORR = 17%; DoR: 3.3-31.1 months; m**PFS (combination arm)** = 12.9 months; **mPFS in KRAS-mutant subset** = 22.0 months, m**PFS in KRAS wild-type subset** = 12.8 months • The FDA also granted Breakthrough Designation for the combination in LGSOC[1]
IMM-6-415 Immuneering	Universal RAS/RAF	Completed in 2025-04-30	**Phase 1b/2** (n=30) NCT06208124	Pancreatic adenocarcinoma, RASmut melanoma, Class I BRAFmut melanoma, RASmut NSCLC, other RASmut GI cancers (aside from CRC)	• The trial was still in early stages; additional patients were being dosed at 320 mg QD in that arm • Ongoing data evaluation
Naporafenib ERASCA	BRAF and CRAF	Phase 3 Ongoing	**Phase 3** (n=470) NCT06346067 **Phase 1** (n=86) NCT05907304	Pan-RAS Q61X tissue agnostic and NRASm melanoma	• **Safety:** Tolerable • **Efficacy:** ORR: 13.3 %; mDOR: ~3.75 months. mPFS: 4.21 months; The "overall" median PFS across expansion cohorts was ~5 mo • Fast Track is in place for naporafenib + trametinib in post-IO NRAS-mutant melanoma[2]

[1] Press release: July11, 2025
[2] Singh et al. (2025). Clin Cancer Res. 31 (8): 1383–1389

MEK Inhibitors

Current clinical stage MEK inhibitors are being assessed in tumors with genetically defined mutations affecting the MAPK pathway

Asset, Company	Target	Next Readout	Phase	Patient Population	Clinical Data To Date
atebimetinib IMM-1-104 Immuneering	MEK	Study Completion (Estimated) 2027-06	**Phase1/2a** (n=209) NCT05585320	Locally advanced unresectable or metastatic tumors: pancreatic ductal adenocarcinoma (PDAC), RAS-mutant melanoma, or RAS-mutant non-small cell lung cancer (NSCLC)	• **Safety:** More than 10% of patients developed the AEs of neutropenia and anemia as in SoC. • **Efficacy** (combined with standard chemotherapy)**:** Phase 2a first-line pancreatic cancer cohort; ORR ~ 37% and DCR: 81%; OS at six months. PFS at six months was 72%[1] • M**onotherapy:** ORR ~ 5% and DCR ~ 52%[2]
REC-4881 Recursion	MEK	2H 2026/1H 2027	**Phase 1/2** NCT05552755 (n=67), NCT06005974 (n=60)	Familial Adenomatous Polyposis (FAP) and AXIN1/APC Mutant Cancers	• **Safety:** AEs were mostly grade 1–2. Grade 3 occurred in ~15.8% of patients. • **Efficacy:** Early readout (small n) showed a ~43% reduction in GI polyp burden at 12 weeks on 4 mg QD; 9/10 evaluable patients maintained reductions in polyp burden, with a 53% median decrease from baseline[3]

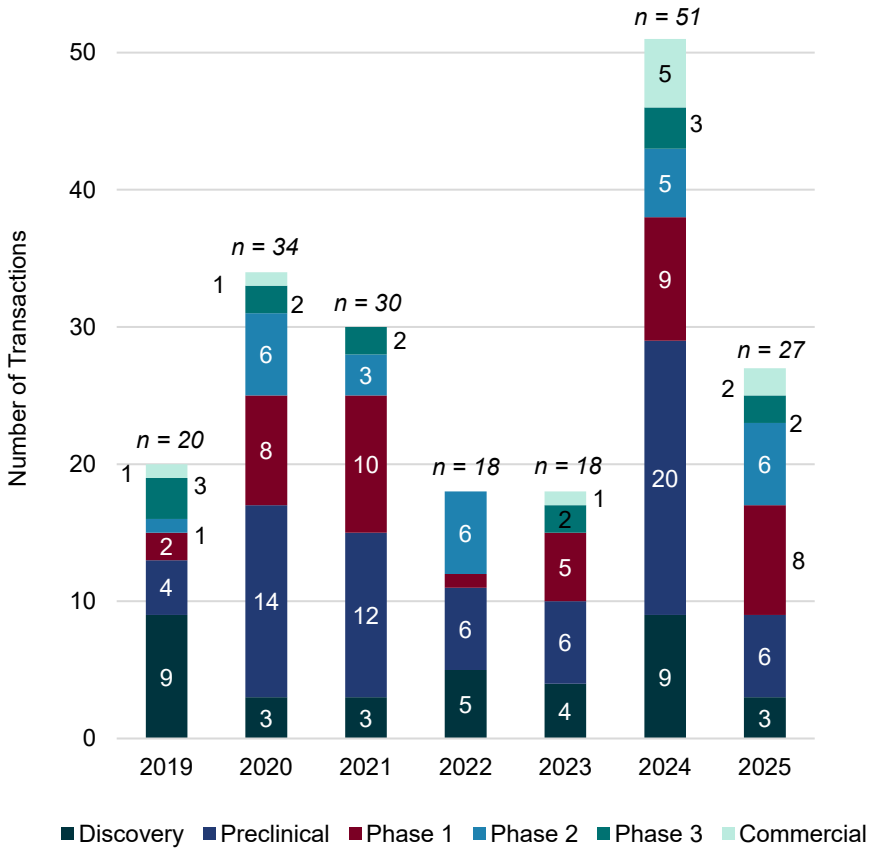
Sources: 1) Company press release, Immuneering, Jun 17, 2025; 2) CancerNetwork, January 8, 2025; 3) Recursion Pharmaceuticals Investor Relations, Dec 8 2025

Transaction Landscape

Precedent Transactions – Small Molecule Targeted Oncology

Since 2019, targeted oncology deal activity has been driven by strategic buyers with early-stage pipeline interest, as more than half of transactions in the space focused on discovery/preclinical stage technology

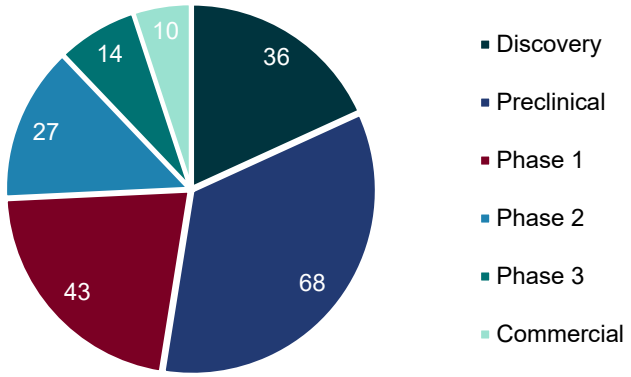
Annual Transactions by Phase (Jan 2019 – Dec 2025)



Key Takeaways

- We identified 198 relevant small molecule targeted oncology deals since 2019
- Strategics are engaging early, with an average of 52% of annual transactions occurring at the discovery or preclinical stage
- Small molecule targeted oncology transactions match general industry trends following the pandemic with an overall decrease in deal volume in 2022 and 2023
  - Additionally, post-pandemic enthusiasm for emerging and novel therapeutic modalities over small molecule approaches likely contributed to this drop
- 2024 saw a spike in deal volume surpassing pre-pandemic volumes by ~33%
  - Preclinical-stage deals dominated the 2024 transaction landscape and approximately 25% of these deals were carried out by big pharma players (e.g., Merck, Bayer, AstraZeneca), demonstrating a revived interest in targeted oncology

Total Transaction Volume by Phase

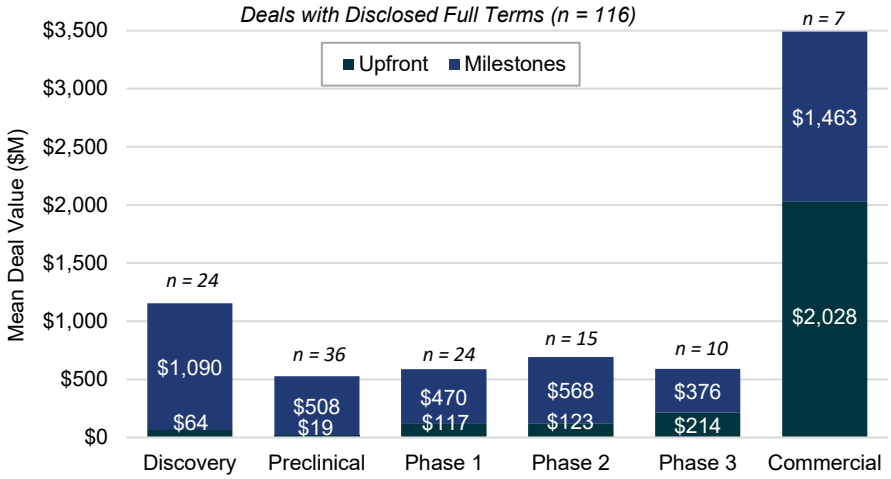


Sources: Back Bay analysis, Company press releases, Cortellis

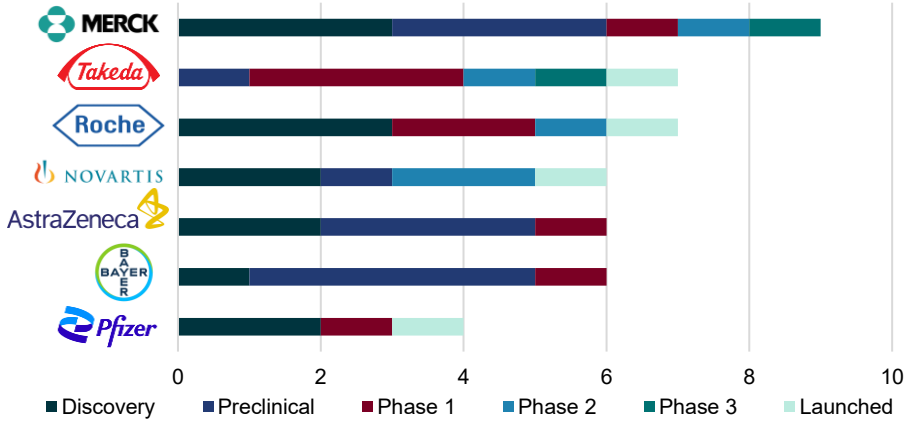
Precedent Transactions – Deal Structure & Strategic Players

Of the $1B+ targeted oncology deals, half occur at the discovery or preclinical stage, reflecting rising appetite for high-value early science as part of broader portfolio diversification

Annual Transactions by Deal Value



Active Strategics ≥4 Deals



Key Takeaways

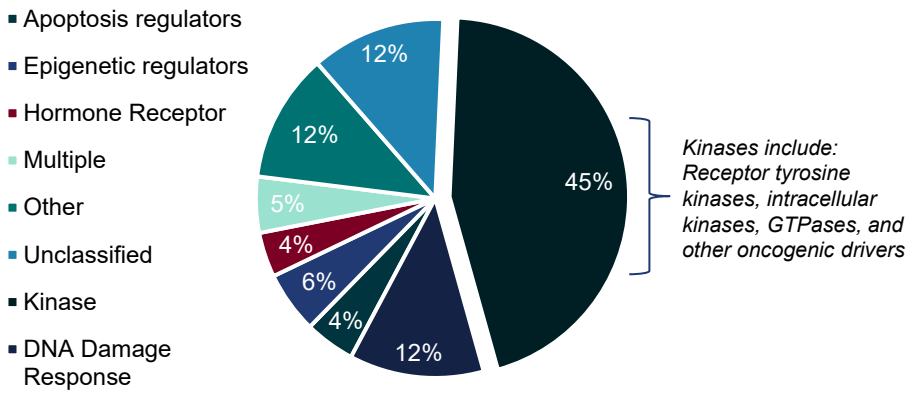
- Small molecule transactions follow broader oncology deal trends, as deal upfronts markedly increase once an asset has reached the clinical stage and is partially de-risked
  - Overall deal values remain consistent through later clinical stages, in contrast to advanced modalities (e.g., ADCs, multispecific Abs), which often see significant valuation step-ups after pivotal data readouts
- Of the top 31 deals >$1B in total deal value (see appendix), ~50% were transacted at the discovery or preclinical stage, indicating willingness from strategics to place larger bets in this space
  - Notably, in 2020 Merck and Taiho Pharma established a strategic oncology collaboration to develop preclinical KRAS-targeting small molecules for $50M upfront and $2.5B in milestones
    - Merck has been an active player in the space overall, with nine relevant transactions since 2019, transactions ranging from the discovery stage to Phase 3 of development
  - In 2024, Roche made two discovery-stage transactions over $1B in deal value through licensing agreements with MOMA Therapeutics and Flare Therapeutics for total deal values of $2.06B and $1.87B, respectively
    - These moves demonstrate Roche's pursuit of "difficult-to-drug" or novel target classes to diversify its pipeline, done so by leveraging external innovation engines rather than only focusing its efforts in-house
- Despite a historical focus and strong positioning in the immuno-oncology space, BMS acquired Mirati Therapeutics for $4.8B upfront ($5.8B total), gaining rights to commercial-stage Krazati (adagrasib), a KRAS G12C inhibitor for NSCLC, the largest deal in this data set
  - The deal helps BMS to build a more balanced oncology portfolio, adding a targeted therapy to hedge against potential headwinds in immuno-oncology

Sources: Back Bay analysis, Company press releases, Cortellis

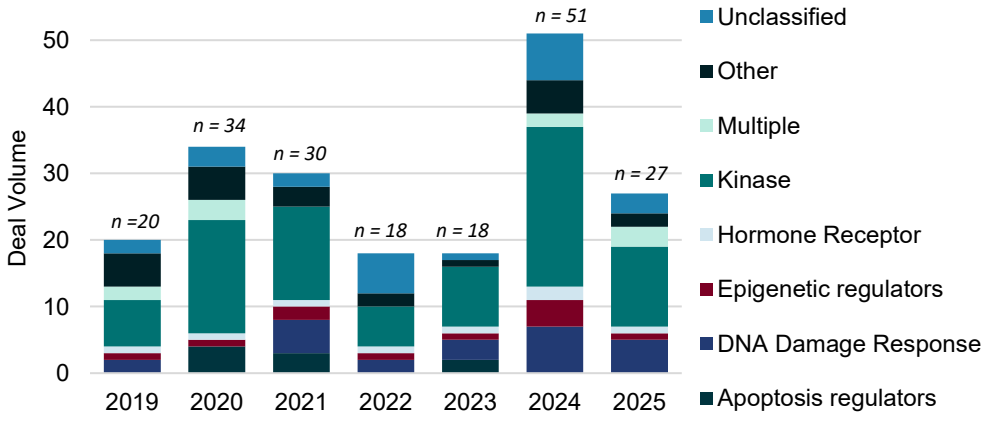
Precedent Transactions – Deals by Target Class

Targeted oncology dealmaking remains heavily kinase-centric, with the RAS/MAPK pathway representing sought-after oncogenic drivers

Deals by Target Class



Deals by Target Class & Year



Deal Volume by Oncogenic Driver Target

Target	Number of Deals
RAS/KRAS	10
RAF/BRAF	7
EGFR	6
MEK/ERK	4

- Kinases dominate targeted oncology dealmaking with 45% (n=89) of all deals involving kinase targets, underscoring that kinases remain a validated and commercially-proven target class in precision oncology
  - Epigenetic regulators, apoptosis regulators, and DNA damage response contribute meaningful slices of deal flow, suggesting a broadening interest in mechanistically novel classes, but most transactions still center around established kinase pathways
- Within kinases, MAPK pathway drivers are a large focus (~30% of kinase deals), reflecting industry belief that oncogenic drivers in this pathway represent both a large commercial opportunity and mark a major scientific inflection point as once "undruggable" nodes have become addressable
  - In 2H25, Bayer and AstraZeneca both participated in deals >$1B to develop and commercialize KRAS inhibitors, emphasizing the importance and potential of targeting this particular oncogene
    - AstraZeneca licensed Jacobio's pan-KRAS inhibitor for $100M upfront leading to ~$2B in total deal value, while Bayer licensed Kumquat Bioscience's KRAS G12D inhibitor for $1.3B total
- The other notable volume of kinase deals involve assets targeting CDK, PI3K, and FLT3 (35% of kinase deals)
  - These targets encompass a variety of cellular processes beyond oncogenic signaling, such as regulation of cell division, metabolism, and drug resistance

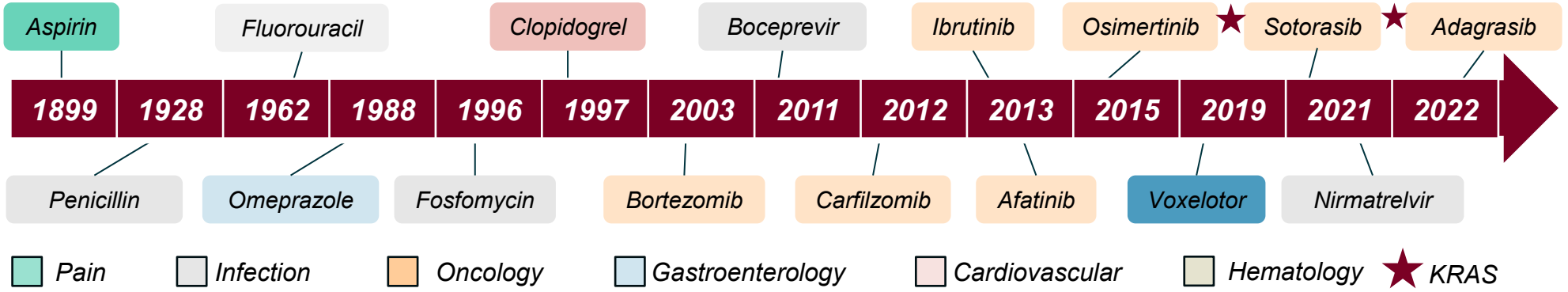
Sources: Back Bay analysis, Company press releases, Cortellis

Emerging Companies and Science-Covalent Modifiers

Covalent Inhibitors – Overview

With the 2013 approval of Ibrutinib (BTK inhibitor) utilization of covalent small molecule inhibitors has seen a rapid increase in pharmaceutical development – including the targeting of KRAS

KEY COVALENT DRUG APPROVALS



History of Covalent Drugs

- Traditional small molecule inhibitors block their target protein through “lock-and-key” or “sticky” approaches, based on conformational fit and reversible chemical interactions such as hydrogen bonds, ionic contacts, and hydrophobic/van der Waals forces result in the molecule blocking the active site of a target molecule
  - As a result, the drug will bind and unbind depending on concentration which necessitates precise dosing of the drug
- In contrast, covalent drugs form a chemical bond to the target resulting in high potency, long target site occupancy, selectivity to mutated amino acid residues, and potential to target surfaces not suitable for other chemistries (e.g., shallow pockets, or those transiently exposed)
- Historically, covalent drugs focused on catalytic serine/cysteine enzymes; however, approaches are expanding to include additional amino acids (e.g., lysine, tyrosine, etc.) as well as reversible approaches to reduce off target effects
  - These approaches constitute trade-offs: for example, cysteine is a well-established target, but resistance mutations emerge, and while other amino acid targets open additional mutants/pathways they come with corresponding selectivity considerations
- In the last decade, there has been increasing attention surrounding covalent inhibitors, with significant interest following the approval of Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, which achieved peak sales of ~$7B in 2021
- ***Shortly after the launch of Ibrutinib, KRAS, which was previously thought to be undruggable, was successfully targeted with covalent inhibition (sotorasib), sparking further interest from large pharma for the development of covalent inhibitors***

Sources: Back Bay analysis, adapted from Boike et al, Advances in covalent drug discovery, Nature Reviews 2022

Covalent Modification – Approaches

Given clinical and commercial success of covalent small molecules, there is growing interest in expanding the chemical toolkit to develop these medicines

Irreversible Covalent Inhibitors

- These approaches rely on chemical entities that once properly positioned in the binding complex, form a permanent bond
  - Advantages include long PD with short PK, strong mutant selectivity (when the targeted residue is mutation-created), and potential to overcome high ATP or cofactor competition

Reversible Covalent Inhibitors

- Reversible covalent inhibitors make an initial temporary chemical interaction with target site, which are stronger than traditional noncovalent interactions, but are intended to eventually release from the target
  - They aim to capture much of the potency/residence benefit of covalent binders while improving safety and enabling finer control of target engagement, dose, and off-target risk

Chemoproteomics

- Chemoproteomics approaches use tagged molecules that allows medicinal chemists to probe which proteins small molecules will bind and then rapidly assess on target and off target binding across thousands of proteins at scale
- This enables identification of novel binding sites to known targets and researchers to assess selectivity of candidate molecules early on the drug development process
- Vetted candidates can then be further optimized using either of the above approaches

Covalent Modifiers

There has been significant venture investment in companies focused on covalent drug discovery, with five companies each raising over $200M+

Company	Last Series	Total Raised to Date (M$)	Investors in Last Round (selected)	Approach/Notes
SCORPION	Series C	420	Atlas Venture, Casdin Capital, Abingworth, Boxer Capital, EcoR1 Capital	Targeted oncology approach and covalent capabilities
vividion THERAPEUTICS	Series C	271	Logos, Boxer, SoftBank IA, Avoro, BlackRock, RA Capital, T. Rowe Price, Surveyor	Photoaffinity/covalent-probe platform
TERREMOTO	Series B	250	OrbiMed, EcoR1 Capital, and Third Rock Ventures	Covalent small-molecule inhibitors
FRONTIER MEDICINES	Series C	235.5	RA Capital, Deerfield Management, Droia Ventures, Galapagos	Scout™ chemoproteomics platform to discover binding ligands
Alterome THERAPEUTICS	Series B	232	Goldman Sachs Alternatives; Canaan, Invus, Driehaus, Digitalis, Blue Owl; OrbiMed, Nextech, Vida, Boxer, Colt	Lysine-targeting reversible-covalent allosteric inhibitors
Enlaza Therapeutics	Series A	161	JPMorgan Life Sciences, Amgen Ventures, Regeneron Ventures, Lightspeed Ventures	Covalent “locking” approach of proteins/biologics
+O+US	Series B	108	Northpond Ventures, DCVC Bio, Camford Capital	Company developing a covalent library + AI irreversible binders
EXO THERAPEUTICS	Series B	103	Nextech Invest; BVF Samsara, Morningside, Casdin; Newpath, Novartis Venture Fund, CRV, 6 Dimensions	Reversible exosite-targeting

Sources: Back Bay analysis, Pitchbook, company website

Covalent Modifiers

Further, early-stage companies have successfully raised private rounds, backed by high-profile life science VC syndicates

Company	Last Series	Total Raised to Date (M$)	Investors in Last Round (selected)	Approach/Notes
matchpoint THERAPEUTICS	Series A	100	Sanofi Ventures, Atlas Venture, Vertex Ventures	Autoimmune focus for covalent chemistries
BridGene Biosciences	Series B+	78.5	Lapam Capital, DYEE Capital, and Junson Capital	IMTAC® chemoproteomics platform to map target sites
REZO	Series A	78	SR One, a16z Bio + Health, Norwest; also SV Angel, Liquid 2, Hawktail	Reversible-covalent lysine-targeting chemistry
nexō therapeutics	Series A	60	Versant Ventures, New Enterprise Associates, Cormorant Asset Management	Covalent-drug discovery company
HYKU BIOSCIENCES	Seed	56	Novartis Venture Fund, Droia Ventures, and RA Capital	Focus on electrophile-enabled irreversible covalent approaches
Belharra THERAPEUTICS	Series A	50	Versant Ventures (founding investor)	Chemoproteomics approach
KYMA THERAPEUTICS	Seed	4.75	I&I Bio; KHAN-II, VORNvc, TU capital	Irreversible covalent-allosteric approaches

Sources: Back Bay analysis, Pitchbook, company website

Covalent Modifiers

There has been increased interest in covalent molecule drug discovery, with large pharma players such as Lilly and Boehringer Ingelheim engaging in early-stage collaborations (1 of 2)

Date	Principal	Partner	Stage	Deal Type	Deal Size	Deal Overview
Sept 2025	Enlaza Therapeutics	VERTEX	Discovery	Discovery Alliance	Upfront: $45M Milestones: >$2B	• Multi-target: covalent biologics for autoimmune disease + conditioning regimens prior to ex vivo C&GT product delivery
July 2025	matchpoint THERAPEUTICS	NOVARTIS	Preclinical	License	Upfront: $60M Milestones: $1B + royalties	• Oral covalent TF inhibitors for inflammatory diseases
Feb 2025	BridGene Biosciences	Takeda	Discovery	License	Upfront & Preclinical payments: $46M Milestones: ~$770M	• Multi-target discovery in immunology & neurology
Jan 2025	SCORPION	Lilly	Phase 1	Asset Acquisition	Up to $2.5B (upfront + milestones)	• Acquisition of STX-478 (PI3Kα) for breast & solid tumors

Sources: Back Bay analysis, Cortellis, Pitchbook, company website

Covalent Modifiers

There has been increased interest in covalent molecule drug discovery, with large pharma players such as Lilly, and Boehringer Ingelheim engaging in early-stage collaborations (2 of 2)

Date	Principal	Partner	Stage	Deal Type	Deal Size	Deal Overview
July 2024	MD Anderson Cancer Center	nexo therapeutics	Discovery	Collaboration	Undisclosed	• Strategic collaboration to develop therapies against previously undruggable targets • Deal incorporates Nexo Therapeutics' drug discovery platform, which combines covalent chemistry and chemical biology
May 2024	+O+US	Lilly	Discovery	Collaboration	Undisclosed	• Collaboration to discover small molecule drug candidates against undisclosed targets • Each party has an exclusive option to develop compounds from the collaboration in exchange for milestones
Jan 2024	BridGene Biosciences	Galápagos	Discovery	License/ Collaboration	Up to $27M in upfront and preclinical milestones	• Collaboration agreement to strengthen Galapagos' early-stage oncology pipeline • The agreement leverages Galapagos' expertise in small molecule drug discovery and BridGene's proprietary IMTAC™ chemoproteomics platform
Apr 2023	SCORPION	Pierre Fabre	Preclinical	License/ Collaboration	Upfront: $65M Milestones: $553M	• Collaboration and license agreement for the co-development of preclinical compounds STX-721 & STX-241 • STX-721 and STX-241 are potentially best-in-class inhibitors of EGFR mutations in development for NSCLC
March 2023	COVANT	Boehringer Ingelheim	Discovery	Collaboration	Upfront: $10M Milestones: $471M	• Agreement to jointly develop a novel small molecule immunotherapy targeting ADAR1 • Covant's platform uses high-throughput chemoproteomics-based screening to develop covalent small molecules

Sources: Back Bay analysis, Cortellis, Pitchbook, company website

Covalent Modifiers

AstraZeneca, Bayer, and AbbVie have all conducted discovery-stage transactions to incorporate assets generated through covalent drug development into their pipelines

Date	Principal	Partner	Stage	Deal Type	Deal Size	Deal Overview
Feb 2023	evotec	RELATED SCIENCES	Discovery	Collaboration	Undisclosed	• Agreement leverages Evotec's capabilities in covalent inhibitor discovery and their custom covalent libraries
July 2022	Scripps Research	bridgebio therapeutics	Discovery	Collaboration	Undisclosed	• Collaboration to discover and characterize novel reactive groups that target non-cysteine residues to uncover new druggable sites • Bridge seeks to discover proprietary, tunable ligands for covalent drug development and protein degrader applications
March 2022	TOTUS	Mila	Discovery	Collaboration	Undisclosed	• Partnership leverages Mila's AI capabilities and Totus' drug discovery tech • Mila is an artificial intelligence research institute that employs over 900 researchers specializing in machine learning
January 2022	SCORPION	AstraZeneca	Discovery	Collaboration	Upfront: $75M Undisclosed milestones	• Collaboration to discover, develop, and commercialize novel cancer treatments against "undruggable" targets • Scorpion's platform uses chemoproteomics and machine learning to identify novel covalent inhibitors for challenging targets
August 2021	vividion THERAPEUTICS	BAYER	Discovery	Acquisition	Upfront: $1.5B Milestones: $500M	• Acquisition intended to strengthen Bayer's drug discovery capabilities with a chemoproteomics platform • Vividion's approach identifies previously unknown binding pockets in undruggable targets to create covalent drugs
Dec 2020	FRONTIER MEDICINES	abbvie	Discovery	Collaboration	Upfront: $55M Undisclosed milestones	• Collaboration to discover and develop a pipeline of small molecule therapeutics against difficult-to-drug protein targets • The deals leverages Frontier's chemoproteomics platform to identify small molecules for programs directed to novel E3 ligases and certain oncology and immunology targets

Sources: Back Bay analysis, Cortellis, Pitchbook, company website

Key Takeaways and Outlook

Data Summary

Multiple key registrational and proof of concept readouts will occur in 2026—particularly in the EGFR and KRAS space

Asset, Company	Target	Trial	Next Readout	Data Type	Patient Population
Daraxonrasib, Revolution Medicines	RAS(ON) multi-selective inhibition	Phase 3	H1 2026	ORR, PFS, OS, DoR, DCR and safety/tolerability	Adults with RAS-mutant advanced solid tumors, including PDAC
Firmonertinib, Arrivent Biopharma	EGFR	Phase 3	H1 2026	PFS, OS, ORR, DOR, Safety	1L NSCLC patients with EGFR exon20 insertions
Silevertinib Black Diamond Therapeutics	EGFR	Phase 2	Q2 2026	ORR, DCR, PFS, DOR and safety/tolerability	LA or metastatic NSCLC harboring non-classical EGFR mutations
Zipalertinib, Taiho Oncology & Taiho Pharmaceutical	EGFR TKI	Phase 3	H2 2026	ORR, PFS, DOR, DCR, safety (RECIST/CTCAE)	Advanced/metastatic NSCLC with EGFR ex20ins or uncommon EGFR mutations
Olomorasib, Eli Lilly	KRAS G12C	Phase 3	Q4 2026	ORR, PFS, OS, DOR, DCR, safety/tolerability, quality of life	Advanced/metastatic NSCLC harboring a KRAS G12C mutation

Sources: Company disclosures

Key Takeaways and Outlook

Despite well-established commercial markets for each target class, these are highly active fields across commercial, clinical, business development, and early-stage R&D functional areas

Early-Stage Launches	▪ JnJ's Lazcluze (Lazertinib), launched in 2024, is a CNS-penetrant, third-generation EGFR TKI positioned in 1L EGFR-mutant NSCLC in combination with amivantamab (Rybrevant) and is at the vanguard of next-generation EGFR regimens and sequencing and commercial success may prove a bellwether for other late-stage assets ▪ In the RAF/MEK/ERK space, Gomekli (mirdametinib, Merck KGaA) and Ojemda (tovorafenib, DayOne) establish a new precedent for pediatric/genetically-defined commercial approaches for MAPK-altered populations and an adoption benchmark for next-gen RAF/MAPK strategies
KRAS Momentum	▪ The KRAS pipeline has scaled rapidly, with ~126 KRAS-directed assets across stages, indicating both strong scientific conviction and increasing competitive density ▪ Development is expanding beyond G12C into G12D, multiallelic/pan-KRAS, and pan-RAS strategies, reflecting an industry shift toward broader addressable populations and deeper pathway control ▪ Multiple 2026 clinical inflection points are expected for leading RAS programs (Daraxonrasib, Revolution Medicines, Olomorasib, Eli Lilly) supporting continued investor and partner focus on the space through key readouts
Deals	▪ Targeted oncology small-molecule BD continues at pace with 198 deals since 2019, approximately ~52% executed at discovery/preclinical, consistent with early partnering behavior in crowded pathways ▪ Momentum has built with large players placing markers on new targets/mechanisms, such as AstraZeneca–Jacobio (Dec 2025) $2B+ exclusive license for JAB-23E73 (Phase 1/2a pan-KRAS inhibitor), reinforcing willingness to pay for breadth and differentiation early in development ▪ Ongoing market speculation regarding potential strategic outcomes for leading RAS-focused companies underscores the perceived scarcity value of scalable RAS franchises ahead of key clinical catalysts (e.g., Revolution Medicines)
Early-Stage Platforms	▪ Platform innovation is accelerating next-wave EGFR–RAS–MAPK programs through irreversible and reversible covalent chemistry and chemoproteomics-driven discovery, expanding druggable residue space and improving selectivity/target engagement profiling ▪ On the heels of substantial capital deployment in a depressed market, a number of private companies (e.g., Scorpion, Vividion, Terremoto, Frontier, Alterome, Totus) are advancing kinase targeting programs in oncology, supporting sustained output of differentiated assets

Appendix

Targeted Oncology Deals with Disclosed Terms

Top 31 deals with total value >$1B from January 2019 through 2025 (1 of 2)

Year	Buyer	Seller	Deal Type	Deal Phase	Target	Upfront ($M)	Total Deal Value ($M) ↓
2024	BMS	Mirati Tx	Acquisition	Launched	KRAS	4,800	5,800
2020	Pfizer	Myovant	License	Launched	GnRH Antagonist	650	4,200
2025	Merck KGaA	Springworks Tx	Acquisition	Launched	Multiple	3,900	3,900
2020	BMS	Schrödinger	Co-development	Discovery	Not specified	55	2,777
2020	Merck	Taiho	License	Preclinical	KRAS	50	2,550
2025	Eli Lilly	Scorpion	Acquisition	Phase 2	PIK3CA	1,000	2,500
2024	ONO Pharma	Deciphera Pharma	Acquisition	Launched	Multiple	2,400	2,400
2019	Gilead	Nurix	License	Discovery	E3 ligases	45	2,345
2025	Genentech	Orion Bio	License	Discovery	Not specified	105	2,105
2024	Roche	MOMA Tx	License	Discovery	Not specified	66	2,066
2022	Sanofi	SkyHawk	License	Discovery	Not specified	54	2,054
2025	AstraZeneca	Jacobio	License	Phase 1	KRAS	100	2,015
2024	Roche	Flare Tx	License	Discovery	Not specified	70	1,870
2024	BeiGene	CSPC Zhonghi	License	Phase 1	MAT2A	150	1,835
2020	Roche	Blueprint	License	Discovery	RET	675	1,602
2022	AstraZeneca	Scorpion	License	Discovery	Not specified	75	1,575

Sources: Back Bay analysis, Company press releases, Cortellis

Targeted Oncology Deals with Disclosed Terms

Top 31 deals with total value >$1B from January 2019 through 2025 (2 of 2)

Year	Buyer	Seller	Deal Type	Deal Phase	Target	Upfront ($M)	Total Deal Value ($M)
2024	Pfizer	TRIANA Bio	License	Discovery	Not specified	49	1,549
2024	Merck	Modifi Bio	Acquisition	Preclinical	MGMT	30	1,330
2022	Roche	Repare	License	Phase 2	ATR	125	1,325
2021	Novartis	Artios	Co-development	Discovery	Not specified	20	1,320
2025	Bayer	Kumquat Bio	License	Preclinical	KRAS	ND	1,300
2023	BeiGene	ENSEM Tx	License	Preclinical	CDK2	ND	1,300
2022	Kirilys Tx	Ube Industries	License	Preclinical	CDK7	ND	1,260
2024	Takeda	Ascentage	License	Launched	BCR-ABL	ND	1,200
2020	Genentech	Relay Tx	License	Phase 1	SHP2	75	1,180
2024	Novartis	Arvinas	License	Phase 2	AR	150	1,160
2025	GSK	IDRx	Acquisition	Phase 2	KIT	1,000	1,150
2023	Takeda	HUTCHMED	License	Phase 3	VEGFR1-3	400	1,130
2021	Merck	Debiopharm	Co-development	Phase 3	Not specified	224	1,070
2025	Novartis	Light Horse Tx	License	Discovery	Not specified	25	1,025
2024	Avenzo Tx	Allorion Tx	License	Phase 1	CDK2	40	1,000

Sources: Back Bay analysis, Company press releases, Cortellis

Important Information – Disclosures

Important Information

The marketing communication (the "Material") is provided for informational and educational purposes only and does not constitute an offer to sell or a solicitation of an offer to buy any securities, nor should it be construed as investment advice. The DNB Carnegie | Back Bay Partnership ("DNB Carnegie | Back Bay") is a marketing term referring to a strategic arrangement between Back Bay Life Science Advisors LLC, a healthcare advisory and investment banking firm ("Back Bay") and DNB Carnegie, a business unit of DNB Bank ASA.

The DNB Carnegie business unit is comprised of: 1) the investment services division of DNB Bank ASA, organized in Norway and regulated by the Norwegian Financial Supervisory Authority; 2) DNB Carnegie Investment Bank AB, a wholly owned subsidiary of DNB Bank ASA, organized in Sweden and regulated by the Swedish Financial Supervisory Authority, and 3) DNB Carnegie, Inc., a wholly owned subsidiary of DNB Bank ASA, incorporated in New York and regulated by FINRA and the Securities and Exchange Commission (collectively, "DNB Carnegie").

The Material has been jointly prepared by the DNB Carnegie | Back Bay Partnership.

The Material is distributed in the U.S. by DNB Carnegie, Inc. and Back Bay; in Norway, Singapore, Canada and Australia by the investment services division of DNB Bank ASA; in Sweden, Finland and Denmark by DNB Carnegie Investment Bank AB; and in the UK by the investment services division of DNB Bank ASA and DNB Carnegie Investment Bank AB, respectively.

Each entity operates independently and provides services within its respective regulatory framework. Any securities-related activities in the U.S. are conducted solely by DNB Carnegie, Inc. for institutional clients.

Securities services offered in the U.S. are offered and sold through DNB Carnegie, Inc. (SEC#8-66024 / CRD# 127605). Additional information for U.S. institutions can be provided by contacting DNB Carnegie, Inc. 30 Hudson Yards, 81st Floor, New York, NY 10001, telephone number +1 212-551-9800.

Property rights

The Material is for clients only, and not intended for re-publication, and has been prepared for information purposes by DNB Carnegie | Back Bay.

Back Bay Life Science Advisors LLC is a Massachusetts limited liability company. Back Bay Life Science Advisory, LLC, a Massachusetts limited liability company, is a wholly owned subsidiary of Back Bay Life Science Advisors LLC.

The Material is the property of DNB Carnegie | Back Bay. DNB Carnegie | Back Bay retains all intellectual property rights (including, but not limited to, copyright) relating to the Material. Sell-side investment firms are not allowed any commercial use (including, but not limited to, reproduction and redistribution) of the Material contents, either partially or in full, without DNB Carnegie | Back Bay's explicit and prior written consent. Use by buy-side investment firms is dependent on the firms citing DNB Carnegie | Back Bay as the source.

The Material does not constitute investment advice

The Material is made for information purposes only and does not constitute and should not in any way be considered as an offer to buy or sell any securities or other financial instruments or to participate in any investment strategy. The Material has been prepared as general information and is therefore not intended as a personal recommendation of particular financial instruments or strategies and does not constitute investment advice. Investors should therefore make their own assessments of whether any of the trading ideas described herein are a suitable investment based on the investor's knowledge and experience, financial situation, and investment objectives.

Risk warning

The risk of investing in financial instruments is generally high. Past performance is not a reliable indicator of future performance, and estimates of future performance are based on assumptions that may not be realized. When investing in financial instruments, the value of the investment may increase or decrease, and the investor may lose all or part of their investment. Careful consideration of possible financial distress should be made before investing in any financial instrument.

Important Information – Disclosures

Author certification

The author(s) responsible for the content of the Material certify that: 1) the views expressed in the Material accurately reflect that author's personal views about the company and the securities that are the subject of the Material; and 2) no part of the author's compensation was, is, or will be, directly or indirectly, related to any views expressed by that author in the Material. DNB Carnegie | Back Bay employees, including authors, may receive compensation that is generated by overall firm profitability.

Potential conflicts of interest

DNB Carnegie | Back Bay may from time to time perform investment banking or other services for, or solicit investment banking or other business from, any company mentioned in this Material. Readers should assume that any company mentioned in this Material may have an active client relationship with DNB Carnegie | Back Bay which is not disclosed due to client confidentiality.

DNB Bank ASA, its affiliates and subsidiaries are engaged in commercial banking activities and may for example be a lender to any company mentioned in the Material. This means that certain parts of these entities might have access to whatever rights and information regarding addressed companies as are available to a creditor under applicable law and the applicable loan and credit agreements.

Back Bay, DNB Carnegie and the rest of DNB Group have implemented a set of rules handling conflicts of interest. This includes confidentiality rules restricting the exchange of information between various parts of Back Bay, DNB Carnegie and the rest of DNB Group. In order to restrict flows of sensitive information, appropriate information barriers have been established between the Investment Banking Division and other business departments in DNB Carnegie, between DNB Carnegie and other business units in the DNB Group, and between the DNB Group and Back Bay. People outside an information barrier may gain access to sensitive information only after having observed applicable wall-crossing procedures. This means that employees of DNB Carnegie who are preparing the Material are prevented from using or being aware of information available in other parts of Back Bay, DNB Carnegie or DNB Group that may be relevant to the recipients' decisions.

Confidential and non-public information regarding Back Bay, DNB Carnegie and the rest of DNB Group and its clients, business activities and other circumstances that could affect the market value of a security ("sensitive information") is kept strictly confidential and may never be used in an undue manner. Internal guidelines are implemented to ensure the integrity and independence of research authors. In accordance with the guidelines, the research department is separated from the Investment Banking department and there are no reporting lines between the research department and Investment Banking. The guidelines also include rules regarding, but not limited to, the following issues: contacts with covered companies, prohibition against offering favorable recommendations, personal involvement in covered companies, participation in investment banking activities, supervision and review of research reports, author reporting lines, and author remuneration.

Each of DNB Carnegie and Back Bay and any of its respective officers or directors may have a position, or otherwise be interested in, transactions in securities that are directly or indirectly the subject of the Material.

Additional information for clients in Australia

The Material has been prepared and issued outside Australia.

DNB Bank ASA ARBN 675 447 702 is exempt from the requirement to hold an Australian financial services licence under the Corporations Act 2001 (Cth) ("Corporations Act") in respect of financial services it provides to "wholesale clients" within the meaning of the Corporations Act ("Wholesale Clients"). DNB Bank ASA accordingly does not hold an Australian financial services licence. DNB Bank ASA is regulated by Finanstilsynet (the Financial Supervisory Authority of Norway) under the laws of Norway, which differ from Australian laws.The Material is provided only to authorized recipients who are both Wholesale Clients and "professional investors" within the meaning of the Corporations Act. In no circumstances may the Material be provided to any other person.

No member of the DNB Group, including DNB Bank ASA and DNB Carnegie Investment Bank AB, or Back Bay is an authorized deposit-taking institution ("ADI") under the Banking Act 1959 (Cth). Accordingly, neither Back Bay, DNB Bank ASA nor DNB Carnegie Investment Bank AB is supervised by the Australian Prudential Regulation Authority as an ADI.

DNB Bank ASA is a public limited liability company incorporated in Norway.

Nothing in the Material excludes, restricts or modifies a statutory warranty or liability to the extent such an exclusion, restriction or modification would be prohibited under Australian law.

Important Information – Disclosures

Additional information for clients In Canada

The Material included herein is marketing material and is not general investment advice. This information is not tailored to the needs of any recipient and, accordingly, is distributed to Canadian residents in reliance on section 8.25 of the Canadian Securities Administrators' National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations.

Additional information for clients in Singapore

The Material is distributed by the Singapore Branch of DNB Bank ASA. It is intended for general circulation and does not take into account the specific investment objectives, financial situation or particular needs of any particular person. Please seek advice from a financial adviser regarding the suitability of any product referred to in the Material, taking into account your specific financial objectives, financial situation or particular needs before making a commitment to purchase any such product or security. You have received a copy of the Material because you have been classified as an accredited investor, an expert investor, or as an institutional investor, as these terms have been defined under Singapore's Financial Advisers Act (Cap. 110) ("FAA") and/or the Financial Advisers Regulations ("FAR"). The Singapore Branch of DNB Bank ASA is a financial adviser exempt from licensing under the FAA but is otherwise subject to the legal requirements of the FAA and of the FAR. By virtue of your status as an accredited investor, institutional investor or as an expert investor, the Singapore Branch of DNB Bank ASA is, with respect to certain of its dealings with you or services rendered to you, exempt from having to comply with certain regulatory requirements of the FAA and FAR, including without limitation, sections 34, 36 and 45 of the FAA. Section 34 of the FAA requires a financial adviser to disclose material information concerning designated investment products that are recommended by the financial adviser to you as the client. Section 36 of the FAA requires a financial adviser to have a reasonable basis for making investment recommendations to you as the client. Section 45 of the FAA requires a financial adviser to include, within any circular or written communications in which they make recommendations concerning securities, a statement of the nature of any interest which the financial adviser (and any person connected or associated with the financial adviser) might have in the securities. Please contact the Singapore branch of DNB Bank ASA at +65 6260 0111 with respect to any matters arising from, or in connection with, the Material. The Material is intended for and is to be circulated only to people who are classified as an accredited investor, an expert investor, or an institutional investor. If you are not an accredited investor, an expert investor or an institutional investor, please contact the Singapore Branch of DNB Bank ASA at +65 6260 0111. DNB Bank ASA, its affiliates and subsidiaries, our associates, officers and/or employees may have interests in any products referred to in the Material by acting in various roles including as distributor, holder of principal positions, adviser or lender. DNB Bank ASA, its affiliates, subsidiaries, our associates, officers and/or employees may receive fees, brokerage or commissions for acting in those capacities. In addition, DNB Bank ASA, its affiliates and subsidiaries, our associates, officers and/or employees may buy or sell products as principal or agent and may effect transactions that are not consistent with the information set out in the Material.

Additional information for clients in the United States

Each person named on the front page of the Material, or at the beginning of any subsection hereof, hereby certifies that (i) the views expressed in this Material accurately reflect that person's personal views; and (ii) no part of the person's compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed in the Material.

This Material is being furnished solely to Major U.S. Institutional Investors within the meaning of Rule 15a-6 under the U.S. Securities Exchange Act of 1934 and to such other U.S. Institutional Investors as DNB Carnegie, Inc. may determine. Distribution to non-Major U.S. Institutional Investors will be made only by DNB Carnegie, Inc., a U.S. broker-dealer and member of the Financial Industry Regulatory Authority ("FINRA") and the Securities Investor Protection Corporation ("SIPC").

Any U.S. recipient of this report seeking to obtain additional information should contact DNB Carnegie, Inc., 30 Hudson Yards, 81st Floor, New York, NY 10001, telephone number +1 212-551-9800.