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Review

Precision oncology in rare tumors: Have the orphans been adopted?

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SUMMARY

Oncology has shifted from organ- or histology-based therapy toward precision medicine, guided by molecular and immune targets. This paradigm change is especially impactful in rare cancers, which may be defined by unusual histology, anatomical site, or uncommon molecular subtypes of common tumors. The emergence of tumor-agnostic, histology-independent classifications has added new molecularly defined rare tumor groups. Biomarker-based therapies mark a turning point in personalized medicine, with several gene- and immune-targeted drugs now approved by the US Food and Drug Administration (FDA). Tissue-agnostic approvals typically rely on trials showing high response rates and durable benefit across diverse cancers driven by rare molecular alterations. This approach is crucial for the ~200 types of histologically rare cancers, where trials in tiny patient subsets are unfeasible. Finally, the complexity and variability of tumor genomics between patients highlight the need for individualized, *n*-of-1 therapeutic combinations as the next step in optimizing cancer treatment.

INTRODUCTION

The standard paradigm of classifying cancers by histology/organ of origin and treating large, unselected groups of patients with the same drugs has shown its limits since the era of molecular biology began.[1] A new approach has emerged over the last two decades, matching molecular alterations with targeted therapies. For targeted agents, biomarker-based trials yield substantially higher response rates and better outcomes than trials of unselected patients.[2,3] Moreover, considering the rarity of many molecular alterations, there is now a disproportionately high number of drugs approved for orphan malignancies compared with medications for the most common tumors, and they often demonstrate high response rates.[4]

Rare cancers are conventionally defined as malignant neoplasms with an annual incidence of <6 cases per 100,000 individuals, a threshold established by the EU-funded Surveillance of Rare Cancers in Europe (RARECARE) program and subsequently endorsed by the Joint Action on Rare Cancers (JARC) and the European Society for Medical Oncology (ESMO).[5–7] Unlike rare non-neoplastic disorders, classified by prevalence, this incidence-based approach has gained international acceptance and is now applied across Europe, the US, and several East Asian countries.[7–9] The US National Cancer Institute employs a more permissive cutoff of <15 cases per 100,000 persons annually.[10]

To capture the end of the spectrum, several groups, including the JARC, have introduced the term "ultra-rare cancer," typically

Box 1. Glossary

ACMG/AMP classification: consensus rules (American College of Medical Genetics/Association for Molecular Pathology) for interpreting sequence variants as pathogenic/likely pathogenic, variant of uncertain significance [VUS], likely benign, or benign.
Agnostic (tumor-agnostic) therapy: drug approval/use based on a shared biomarker across cancers, independent of tissue of origin (e.g., MSI-H/dMMR or NTRK fusion).
Basket trial: one investigational therapy (or combination) is tested across multiple tumor types that share a common biomarker; each "basket" (histology) is analyzed separately.
Chromothripsis: catastrophic genome rearrangement in which one or a few chromosomes shatter and are reassembled, leaving a characteristic copy-number/signature pattern.
EMA/FDA/MHRA/PMDA/Swissmedic: European, US, UK, Japanese, and Swiss medicines regulators, respectively.
ESCAT: ESMO scale for clinical actionability of molecular targets; ranks biomarker-drug matches (tier I/II = highest clinical actionability).
LOH (HRD assays): loss-of-heterozygosity metrics used to infer homologous recombination deficiency; cutoffs are assay specific and not interchangeable.
HRD (homologous recombination deficiency): impaired DNA double-strand break repair (e.g., BRCA1/2 dysfunction) that may predict sensitivity to PARP inhibitors; assays and thresholds vary by platform and tumor type.
HTA (health-technology assessment): post-regulatory appraisal of clinical and cost-effectiveness that informs national reimbursement decisions.
Master protocol: an overarching clinical trial framework that can host basket, umbrella, and/or platform components under a single protocol.
Molecular tumor board (MTB): a multidisciplinary forum that interprets sequencing results and issues treatment/trial recommendations; often provides patient-facing summaries.
NCCN Compendium: US reference used by Medicare/private payers to reimburse guideline-supported off-label uses (typically level 2A evidence).
***n*-of-1 trial**: *N* of 1 in oncology trials refers to those in which each patient is treated with an individualized biomarker-based regimen, which often includes combination therapies.
Platform trial: adaptive, perpetual trial with a shared control arm; treatment arms can be added or dropped based on interim analyses.
Real-world evidence (RWE)/registries: clinical data collected outside traditional trials (e.g., DRUP and national registries) used to evaluate effectiveness, safety, and access.
Umbrella trial: multiple targeted agents tested within a single cancer type, with assignment by distinct biomarker subgroups.
VUS: a genetic alteration with insufficient/conflicting evidence for pathogenicity; not actionable without additional data.

referring to malignancies with an incidence of $\leq$1 per 50,000 population ($\approx \leq$1,000 new cases per year in the US).[6,11] For some tumor families, even lower thresholds are endorsed; for instance, the Connective Tissue Oncology Society designates soft-tissue sarcomas with an incidence of $\leq$1 per 1,000,000/year as "ultra-rare sarcomas."[12] These tumors often qualify as orphan diseases under the US Orphan Drug Act because the expected market is insufficient to recoup development costs.

The definition of targeted therapy is more complex. Still, it can indicate drugs or other agents that target a specific gene product or pathway or an immune moiety. In retrospect, even cytotoxic agents often have a "target," even though that target was usually not identified as a biomarker due to technological limitations at the time of development of the chemotherapy.[13] Sometimes, a targeted therapy may have multiple targets simultaneously, as seen with multi-kinase inhibitors. Targeted therapies have had numerous success stories and have revolutionized the treatment paradigm. Still, it is essential to acknowledge that these drugs work best when administered to patients with a corresponding biomarker.[2] Biomarker-matched targeted drugs have remarkably improved outcomes both in rare malignancies, such as gastrointestinal stromal tumors (GISTs), and in rare subsets of more common tumors, such as non-small cell lung cancer (NSCLC), in which epidermal growth factor receptor (EGFR), ALK (anaplastic lymphoma kinase), and MET (MNNG HOS transforming gene) inhibitors are examples of numerous oncogene-matched approaches, with almost 70% of NSCLCs now representing a biomarker-matchable subgroup.[14] It is now becoming clearer that stratifying common tumors into smaller molecular groups and, in doing so, into many "rare diseases," may optimize diagnostic classification. Moreover, the ultimate stratification may be *N* of 1, treating each tumor and patient in a precise/personalized manner.

There are estimated to be ~200 types of rare/ultra-rare cancers.[5,15] Although individually uncommon by definition, rare cancers constitute >20% of the cancer burden. Randomized controlled trials for rare or ultra-rare cancers are often infeasible, and patients with rare vs. more common tumors may have a poorer prognosis due to late or incorrect diagnosis and fewer available treatment options. Historically, patients with rare conditions have not been well served by drug development, as it has been difficult to recoup the costs of creating and bringing new drugs to market. Hence, in 1983, in the US, the Orphan Drug Act incentivized pharmaceutical companies to pursue drugs for rare diseases by offering market exclusivity and tax credits. The Act proved remarkably effective. In the past four decades, >180 rare cancers have had at least one compound that has been developed and shown promise in its treatment, diagnosis, or prevention. Rare hematologic malignancies were the most commonly impacted, but an orphan-drug-designated agent represented nearly every organ system.[16,17]

In the meantime, our understanding of cancer was also transformed. Indeed, it is now known that cancers are driven by their underlying molecular alterations, and this understanding created a new biomarker-based nosology. This new classification enabled more effective therapies and generated rare or ultra-rare cancer types. Biomarker-based therapeutic paradigms are the cornerstone of precision/personalized medicine, aiming to move from a one-size-fits-all approach to individualized treatment that is more cost-effective, results in fewer side effects, and has better outcomes.

The breakthrough concept of biomarker-driven tumor-agnostic therapy (Box 1) was formalized in 2017 when the anti-PD1 immunotherapy pembrolizumab was approved by the US Food and Drug Administration (FDA) for microsatellite-instability-high (MSI-H)/deficient mismatch repair (dMMR) solid cancers. The FDA has issued multiple tumor-agnostic solid cancer approvals[18–27] (Table 1). These approvals have been based on

Table 1. An overview of FDA-approved tumor-agnostic therapies

Mechanism	Drug	Target	FDA approval year	Approximate number of patients cited by FDA approval summary	ORR	Type of cancer	Percentage of cancers with anomaly	Includes children	Comment	Reference
PD-1 checkpoint blockade immunotherapy	pembrolizumab	MSI-H/dMMR	2017	149	39.6%	solid cancers; included biliary tract cancers	~3%	yes	first tissue-agnostic approval	FDA approval[20]
	pembrolizumab	TMB-H $\geq$ 10 mutations/mb	2020	102	29%	solid cancers; included biliary tract cancers, NETs, thyroid cancers	~14%	yes	–	FDA approval[21]
	dostarlimab	dMMR	2021	209	41.6%	solid cancers; included biliary tract cancers, rare ovarian subtypes, sarcomas, CUP	~3%	no	–	FDA approval[29]
NTRK inhibitors	larotrectinib	*NTRK* fusions	2018	55	75%	solid cancers; included GISTs, STS, biliary tract cancers, rare subtypes of common cancers	~0.3%	yes	–	FDA approval[22]
	entrectinib	*NTRK* fusions	2019	54	57%	solid cancers; included: sarcomas, CNS tumors, biliary tract cancers, rare subtypes of common tumors	~0.3%	yes	–	FDA approval[23]
	repotrectinib	*NTRK* fusions	2024	88	50%–58%	solid cancers; included: sarcomas, CNS tumors, biliary tract cancers, rare subtypes of common tumors	~0.3%	yes	–	FDA approval[24]
RET inhibitor	selpercatinib	*RET* fusions	2022 and 2024	41	44%	solid cancers; included sarcomas, cholangiocarcinoma, thyroid cancers, CUP, CNS tumors	~0.7%	yes	initial approval in 2022 for adults; in 2024, expanded to children $\geq$2 years old	FDA approval[25]

(*Continued on next page*)

Table 1. ***Continued***

Mechanism	Drug	Target	FDA approval year	Approximate number of patients cited by FDA approval summary	ORR	Type of cancer	Percentage of cancers with anomaly	Includes children	Comment	Reference
BRAF/MEK inhibitor	dabrafenib plus trametinib	*BRAF V600E* mutations	2022	131	41%	solid cancers; included ATC, CNS tumor, biliary tract cancers, sarcomas	~3%	yes	colorectal cancer excluded from approval	FDA approval[26]
HER2 antibody-drug conjugate with topoisomerase 1 inhibitor payload	trastuzumab deruxtecan	HER2 3+ IHC	2024	192	50%	solid cancers; included biliary tract cancers, CUP; rare subtypes of common tumors	~3%	no	–	FDA approval[27]
FGFR inhibitor	pemigatinib	*FGFR1* rearrangement	2022	28	79% complete cytogenetic response rate	myeloid/lymphoid hematologic neoplasms	ultra-rare	no	first tissue-agnostic approval for a blood cancer	FDA approval[18]

dMMR, deficient mismatch repair; FDA, US Food and Drug Administration; MSI-H, microsatellite instability high; TMB-H, tumor mutational burden high; ORR, overall response rate; ATC, anaplastic thyroid cancer; CNS, central nervous system; CUP, cancer of unknown primary; IHC, immunohistochemistry; NETs, neuroendocrine tumors; STS, soft-tissue sarcoma; RET, rearranged during transfection

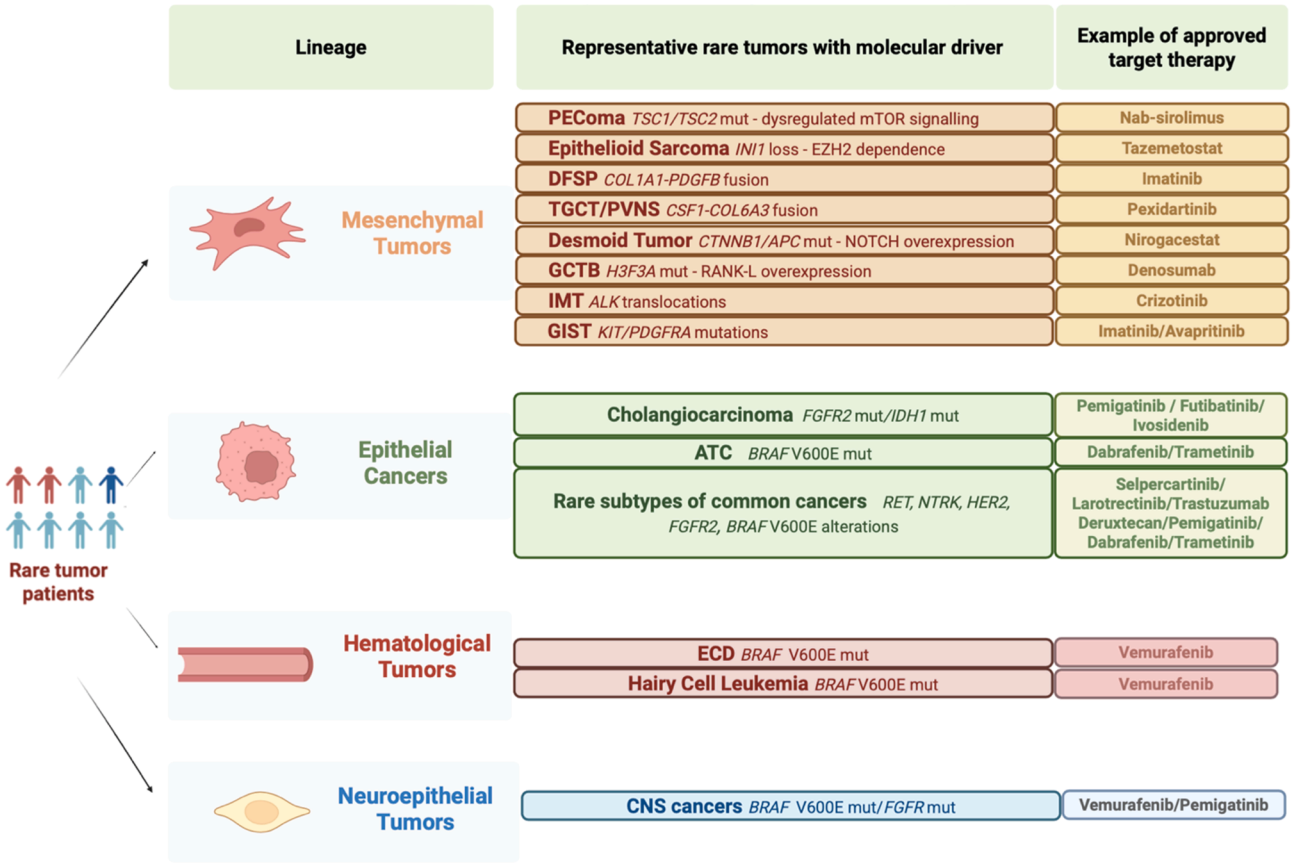

Figure 1. Rare tumors by lineage: Selected examples, molecular features, and approved targeted treatments

DFSP, dermatofibrosarcoma protuberans; TCGT/PVNS, tenosynovial giant cell tumor/pigmented villonodular synovitis; GCTB, giant cell tumor of bone; IMT, inflammatory myofibroblastic tumors; GIST, gastrointestinal stromal tumors; ATC, anaplastic thyroid cancer; ECD, Erdheim-Chester disease.

high response rates with remarkable durability found in small groups of biomarker-selected patients (often ~30–100 individuals in clinical trials). The approvals, along National Comprehensive Cancer Network (NCCN) guideline amendments, have been a great boon to the underserved patients with rare cancers for whom clinical trials aimed at a rare biomarker-defined molecular subgroup of each of the ~200 rare cancers would be virtually impossible to conduct[28] and have assured that even patients with the least common forms of cancer have access to tailored, cutting-edge care.

Herein, we discuss the landscape of rare and ultra-rare cancers. In the molecular era, the evolving definition of "rare" can include (1) the ~200 malignancies that are rare as established by conventional light-microscopy-based histology/organ-of-origin classifications (and which can at times be characterized by a single molecular driver, such as *BRAF* V600E mutations in hairy cell leukemia [HCL]); (2) molecularly defined subgroups of common tumors, perhaps epitomized by lung cancer (with small subsets of patients having *ALK*, *BRAF*, *HER2*, *RET*, *MET*, or other alterations); (3) molecularly defined, tumor-agnostic cancers, now with multiple FDA approvals (e.g., neurotrophic tyrosine receptor kinase [*NTRK*] fusions, *RET* altered, and *BRAF* V600E mutated); and (4) the culmination of rare nosology in recognition that, at the molecular level, metastatic cancers are each unique and complex and thus akin to malignant snowflakes or one of a kind. Throughout this manuscript, we refer to a cancer as rare when it affects fewer than 6 people per 100,000 each year, unless otherwise noted. We next highlight several histology-agnostic molecular drivers, such as *NTRK* fusions, *RET* rearrangements, and *BRAF* V600E, because drugs against these targets have become central to treating many traditional rare and ultra-rare tumors. In contrast, we do not revisit the small biomarker-positive niches within otherwise common cancers; those are reviewed in detail elsewhere.[30]

RARE TUMORS WITH ACTIONABLE DRIVERS

Multiple rare tumors now have actionable drivers (Figure 1) and very high response rates. Indeed, the pathophysiologic basis for a cancer being rare may be the same as the reason that it may ultimately be so treatable. That is, if cancer can be derived only via a single aberrant molecular genetic aberration, then it should be both rare and easily targeted by a molecular cancer therapeutic approach. If, on the other hand, many distinct pathways can lead to the development of a specific tumor type, it should occur much more commonly and be significantly

more challenging to treat.[4] We describe examples of rare cancers with actionable molecular drivers and compounds that have reached regulatory approval based on remarkable efficacy that results from targeting the effects of specific molecular anomalies.

GISTs

GISTs are rare mesenchymal neoplasms of the gastrointestinal tract. The yearly incidence is 6.78 per million. Most GISTs are sporadic, but about 5% are part of familial forms. *GIST*s generally arise in the interstitial cells of Cajal of the stomach and small intestine, although they can occur at any level of the digestive tract. When localized, surgery is a curative option. Approximately 25% of gastric GISTs and 40%–50% of small intestinal GISTs are clinically aggressive; 10%–25% of patients present with metastatic disease. Before the introduction of tyrosine kinase inhibitors (TKIs) such as imatinib, the overall survival (OS) of patients with advanced or metastatic GISTs was only 10–20 months because of the lack of approved therapies and near-zero response rate to chemotherapy. Biomarker-based therapy revolutionized outcomes for GIST, starting with the first patient treated with imatinib.[31] Remarkably, positron emission tomography (PET) imaging may detect decreased tumor avidity after imatinib in GISTs as soon as 24 h after the first dose. GISTs are characterized mainly by mutations in the *KIT* gene (~69%–83% of patients), but other mutations can also occur, such as those in *PDGFR* (platelet-derived growth factor receptor)-alpha (~5%–10% of patients). The ~15% of GISTs without *KIT*/*PDGFRA* mutations are heterogeneous. The most common *KIT* mutation occurs in exon 11 (~66%), whereas the most common *PDGFRA* mutation occurs in exon 18. These primary mutations are mostly mutually exclusive, such that primary tumors have either a *KIT* mutation or a *PDGFRA* mutation but generally not both. However, patients may have >1 mutation in the same gene because they develop secondary resistance mutations while on treatment. Some patients have mutations in other genes, such as *BRAF*, *NTRK*, and succinate dehydrogenase (*SDH*), and can be treated with a cognate inhibitor, which exists for all these alterations except *SDH*; germline *KIT*, *SDH*, *NF1*, and *PDGFR* alterations can also be associated with GIST.[32,33]

Targeted therapies are the standard first-line treatment in the advanced setting. Imatinib is an inhibitor of KIT, PDGFRA, and breakpoint cluster region-Abelson murine leukemia (BCR-ABL) tyrosine kinase and is used to treat inoperable or metastatic GISTs. The standard dosage is 400 mg for all sensitive mutations. *KIT* exon 9 mutations are treated with 800 mg/day, as this provides longer progression-free survival (PFS). In the second line, ~67% of patients have >1 secondary mutations involving *KIT* exons 17, 13, and 14, causing resistance to imatinib. Point mutations associated with imatinib resistance are usually located in the drug/ATP binding pocket of the receptor (encoded by exons 13 and 14) or in the activation loop (encoded by exon 17).[34] In the second line, sunitinib was approved after a phase 3 trial in patients with GISTs failing or intolerant to imatinib. It showed a longer PFS (27.3 vs. 6.4 weeks) in patients treated with sunitinib than placebo. Higher response rates were observed among GISTs with a primary *KIT* exon 9 mutation. Sunitinib has little activity against secondary mutations involving the *KIT* activation loop (exons 17 and 18).[35] In the third line, regorafenib, a multi-kinase inhibitor, demonstrated a significant improvement in median PFS (4.8 vs. 0.9 months) compared to placebo in patients who had already received treatment with imatinib and sunitinib, leading to its approval. It has become the treatment of choice in patients with *KIT* exon 17 mutations, as these do not respond to sunitinib.[36,37] Ripretinib is a TKI that targets *KIT*, *PDGFRA*, *PDGFRB*, *VEGFR2*, and *BRAF*. The INVICTUS trial included 129 participants with advanced GISTs who had progressed after treatment with imatinib, sunitinib, and regorafenib. Ripretinib significantly improved PFS and OS compared to placebo (15.1 vs. 6.6 months).[38] Doubling the dose (2 × 150 mg) upon first progression on the standard dose led to an additional gain in PFS of 3.7 months.[39] Furthermore, ripretinib demonstrated a PFS benefit regardless of the primary mutation.[40] In the second-line INTRIGUE trial against sunitinib, ripretinib did not improve PFS but did improve response rates (23.9 vs. 14.6%). Sunitinib showed better PFS in the exon 9 subgroup.[41] Notably, a phase 2 study in China testing ripretinib in the second line demonstrated a PFS benefit.[42] The VOYAGER trial, a phase 3 randomized study, compared avapritinib with regorafenib as third-line therapy. No significant differences were observed in patients who were not molecularly selected. Still, in the subgroup of patients with the PDGFRA exon 18 D842V mutation, which is known to be resistant to other TKIs, avapritinib demonstrated high response rates and is approved in this indication.[43] These findings echo the earlier phase 1 NAVIGATOR study, which also recorded a high response rate in D842V-mutant disease.[44] In the last 20 years, the treatment algorithm for patients with advanced GISTs has evolved and now includes the KIT multi-kinase inhibitors imatinib, sunitinib, and regorafenib as first-, second, and third-line therapies, respectively; ripretinib (also a KIT inhibitor) is used for fourth-line therapy; and avapritinib is used for first-line therapy in patients harboring *PDGFRA* exon 18 D842V mutations. Imatinib will be less effective and is therefore not recommended in cases of a *PDGFRA* D842V mutation or an SDH-deficient-related GIST. Imatinib, sunitinib, regorafenib, and ripretinib are approved by both the FDA and European Medicines Agency (EMA) for advanced GISTs irrespective of genotype, whereas avapritinib is authorized only for tumors bearing *PDGFRA* exon 18 mutations (e.g., D842V). Accordingly, genotype-directed TKIs remain the first-line standard, with the drug choice or dose tailored to the specific KIT or PDGFRA variant.

Liquid-biopsy circulating tumor DNA (ctDNA) profiling can now reveal secondary resistance mutations, ATP binding pocket (*KIT* exon 13/14) vs. activation loop (exon 17/18) alterations, and rarer events, such as *FGFR2* fusions or PI3K pathway lesions.[45] The phase 3 INSIGHT trial[46] is the first to allocate second-line therapy by ctDNA, randomizing post-imatinib patients with activation loop mutations between ripretinib and sunitinib.

Perivascular epithelioid cell tumors

Perivascular epithelial cell tumors (PEComas) comprise a family of rare mesenchymal tumors composed of "perivascular epithelioid cells" with melanocyte and smooth muscle differentiation.

They can occur anywhere in the body, but their most common forms are renal angiomyolipoma and pulmonary lymphoangioleiomyomatosis (LAM). They are often associated with the tuberous sclerosis complex and can arise in the uterus, gastrointestinal tract, retroperitoneum, or soft tissues adjacent to blood vessels.[47] These tumors can exhibit aggressive behavior, frequently leading to both local recurrences and distant metastases, primarily within the lungs.[48] Additionally, PEComas are generally chemotherapy resistant.[49]

At the molecular level, PEComas are characterized by *TSC1* or *TSC2* mutations, *TFE3* gene fusions, or *FLCN* truncating mutations. Mutations in the *TSC1* or *TSC2* genes, whether germline or sporadic, disrupt the mTOR signaling pathway,[50] contributing to the pathogenesis of the disease. The AMPECT trial, a phase 2 study with an open-label design, evaluated the efficacy of nab-sirolimus, an mTOR pathway inhibitor, in a cohort of 31 patients with advanced PEComas.[51] The overall response rate (ORR) was 39% (12/31; 95% confidence interval [CI], 22–58), including one complete and eleven partial responses. Patients harboring mutations in the *TSC2* gene were more likely to respond to nab-sirolimus. Among responders, 67% had a response lasting greater >12 months, and 58% had a response lasting >24 months. On this basis, in 2021, the FDA approved nab-sirolimus for PEComas. To note, earlier-generation mTOR inhibitors such as sirolimus and everolimus have also demonstrated clinical activity in PEComas, as reported in retrospective series and case reports,[52] further supporting the therapeutic relevance of mTOR pathway inhibition in this tumor type.

Inflammatory myofibroblastic tumors

Inflammatory myofibroblastic tumors (IMTs) are a rare type of mesenchymal neoplasm that primarily affects adolescents and young adults. They usually originate in the lungs, retroperitoneum, or abdominopelvic region. Distant metastases are uncommon and mostly appear in the lung, brain, and liver, especially in ALK-negative IMTs. IMTs are classified as soft-tissue tumors with intermediate biological potential, with only a tiny proportion displaying aggressive behavior.[53] In unresectable cases, no standard treatment is known. While chemotherapy with anthracyclines might be an option, patients with advanced/unresectable or metastatic IMTs are typically resistant to standard chemotherapy agents.

Approximately 50% of IMTs exhibit *ALK* translocations (with a variety of fusion partners).[54,55] Moreover, IMTs may rarely harbor *NTRK* fusions.[56] In 2022, the FDA approved the ALK inhibitor crizotinib for IMTs for adult and pediatric patients (>1 year old) with unresectable, recurrent, or refractory ALK-positive IMTs[57] following the positive results of a prospective, multicenter, phase 1/2 study of crizotinib in children and young adults with ALK-positive solid tumors that reported an ORR of 86% and durable responses exceeding 2 years in the majority of responders.[58] The biomarker-driven, multicenter EORTC 90101 "CREATE" phase 2 basket trial treated 20 patients with advanced IMTs using crizotinib. In the ALK-positive cohort, the ORR was 66.7% with a median PFS of 18 months.[59] Other ALK inhibitors, such as alectinib or brigatinib, have shown activity, but data are limited.[60] NTRK inhibitors are active in the rare cases of tumors containing *NTRK* gene fusions. Larotrectinib or entrectinib can be offered, as durable responses have been reported, including complete remissions lasting over 3.7 and 4.8 years in two patients with lung IMTs and another patient with peritoneal IMTs who achieved a complete response for over 10 months following neoadjuvant larotrectinib.[61,62]

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) is a type of soft tissue sarcoma commonly occurring in the skin. Although most cases of DFSP are low grade, about 10%–15% have a higher-grade sarcomatous component.[63] The characteristic chromosomal translocation t(17;22) is present in DFSP, resulting in the constitutive activation of PDGFRB through the COL1A1 promoter (*COL1A1-PDGFB* fusion). When metastatic, data suggest a lack of responsiveness to classic chemotherapy.[64] Targeted therapies must be offered as first-line treatment when systemic management is needed. A systematic review of nine studies involving 152 patients treated with imatinib (a multi-kinase inhibitor that suppresses PDGFR activity) for advanced or metastatic DFSP showed that 91% of treated patients had a t(17;22) translocation, and ~60% attained an objective response.[65] DFSP with fibrosarcomatous transformation may have a shorter time to recurrence.[66] In 2005, the FDA approved imatinib for adult patients with unresectable, recurrent, and/or metastatic DFSP.

Tenosynovial giant cell tumors

Tenosynovial giant cell tumors (TGCTs) are also called pigmented villonodular synovitis (PVNS); it is an uncommon proliferative disorder of the synovial tissue. The primary concern with TGCTs is local recurrence, as metastases are rare.[67] A fusion in *CSF1-COL6A3* is responsible for the overexpression of colony-stimulating factor-1 (CSF-1) and the recruitment of macrophages expressing the CSF-1 receptor, which is a hallmark of TGCT.[68] At recurrence, surgery and radiation therapy can be offered to limit local invasion and functional damage. Pexidartinib, a CSF-1R inhibitor, was tested in a randomized, double-blinded, phase 3 trial (ENLIVEN) enrolling 120 patients with TGCT. It showed a response rate of 38% (including 15% complete responses), compared to 0% in the placebo group, a duration of response of 46.8 months,[69] and improved functional outcomes. The FDA, therefore, approved pexidartinib for TGCTs in 2019. However, severe hepatotoxicity is possible, and careful monitoring of liver function tests is required.[70] Emactuzumab is a monoclonal antibody that inhibits CSF1R activation. In a phase 1 trial, a response rate of 71% in 68 patients with advanced TCGTs[71,72] was demonstrated. A randomized, phase 3 trial is ongoing (ClinicalTrials.gov: NCT05417789).

Giant cell tumor of bone

Giant cell tumor of bone (GCTB) is a locally aggressive osteolytic skeletal tumor typically occurring in young adults. While malignant transformation of GCTB is rare, lung metastases have been reported. GCTB constitutes ~3%–5% of all primary bone tumors. A known risk factor for GCTB is Paget disease of bone. The *H3F3A* gene is mutated in over 90% of GCTB cases, but its mechanistic connection to tumor pathogenesis is uncertain.[73] On a histological level, GCTB features a high

concentration of osteoclast-like giant cells, which interact with a group of mononuclear cells. The mononuclear cells use receptor activator of nuclear factor κB (NF-κB) and its ligand (RANK/RANKL) signaling to recruit giant cells, with tumor cells expressing RANK-L. Through cytokine secretion, these cells can attract histiocytes and osteoclasts via their RANK receptor.[74] Surgical resection, radiotherapy, and observation are options.[75]

Denosumab is a monoclonal antibody that binds to RANKL and competitively inhibits its binding to RANK. It was tested in a phase 2 trial among 37 patients with recurrent, unresectable, or metastatic GCTB, and 86% of patients had a tumor response.[76] In 2013, the FDA approved denosumab for this indication, and the EMA approved it in September 2014. Side effects may include hypocalcemia and osteonecrosis of the jaw. These tumors may also undergo transformation to sarcoma, albeit rarely, and the risk seems about equivalent with or without denosumab therapy.[77]

Desmoid tumors

Desmoid tumors are ultra-rare, soft-tissue tumors affecting 3–5 persons per million annually. Although they have no known potential for metastases or dedifferentiation, they can be locally aggressive and invasive, leading to morbidity and even death. They can have an unpredictable disease course, with spontaneous regression seen in up to 20%–30% of patients.[78] Treatment may vary depending on the situation and clinical evolution and includes periods of active surveillance, surgery, local therapies, and systemic treatments.[79] Post-surgical recurrence rates of up to 50%–88% are observed, especially in patients with familial adenomatous polyposis (FAP).[80,81] Indications for systemic therapy are unresectable desmoids that are symptomatic, multiple locoregional recurrences, and symptomatic tumors for which surgery would be too morbid or symptomatic mesenteric localization. 90% of sporadic desmoid tumors carry genetic mutations in the *CTNNB1* gene, and 10% of patients with FAP carry a mutation in *APC*.[82,83] Desmoid tumors express NOTCH1, with crosstalk between these pathways resulting in overactivation of the NOTCH pathway.[84–86] A double-blind, placebo-controlled, phase 3 trial was conducted with 142 patients to test nirogacestat, an oral gamma secretase inhibitor that targets gain of function in the NOTCH pathway. At a median follow-up of 19 months, nirogacestat improved PFS (median not reached vs. 15 months), ORR (41% vs. 8%), and complete response (7% vs. 0%) rates compared to placebo.[87] In addition, nirogacestat resulted in improvement in tumor-related symptoms and quality of life. Of note, ovarian dysfunction was observed in most patients of reproductive age, but it mostly resolved after treatment discontinuation. This is particularly relevant for a disease that predominantly affects young women.[87] Tegavivint is a selective nuclear β-catenin degrader and TBL1 inhibitor that targets the WNT signaling pathway implicated in the molecular pathogenesis of desmoid tumors. A phase 1 trial investigating its efficacy in unresectable desmoid tumors showed an ORR of 25%. Further studies are necessary to investigate its therapeutic potential.[88] Interestingly, sorafenib (a drug with putative WNT inhibitor activity[89]) showed a 25% ORR.[90] Taken together, these data suggest that targeting the WNT pathway with specific inhibitors in desmoid tumors can be effective.[91] In 2023, the FDA approved nirogacestat for adult patients with progressive desmoid tumors who require systemic treatment.

Epithelioid sarcomas

Epithelioid sarcomas (ESs) make up approximately 1% of all sarcomas. ESs may arise within a syndromic context, such as Li Fraumeni and retinoblastoma, or due to radiation exposure. More than 90% of tumors have INI1 expression loss, which results in oncogenic dependence on the transcriptional repressor EZH2.[92] For patients with locally advanced or metastatic ESs, ineligible for complete surgical resection, and with aggressive disease that requires a rapid response, doxorubicin is the first choice, either as a single agent or in combination with ifosfamide. Alternative treatment options include gemcitabine plus docetaxel or vinorelbine.[93] Given the tumor dependency on activating enhancers of EZH2 activity, an inhibitor of EZH2, tazemetostat, was tested in the phase 2 EZH-202 trial, which included 62 patients with advanced ESs with INI1 loss.[92] The ORR was 15% (95% CI, 7%–26%), and 1.6% had complete responses. This led to an FDA accelerated approval in 2020.

Anaplastic thyroid cancer

Anaplastic thyroid cancer (ATC) is one of the most aggressive types of malignant tumors, historically offering a median OS of just 5 months.[94] This already challenging situation is further complicated by the rarity of the disease, which has traditionally limited treatment options. ATC is responsible for nearly half of all deaths related to thyroid cancer and is known for its rapid growth, invasion of nearby structures, and early metastasis. Consequently, early diagnosis, staging, and treatment are crucial. While most oncologists will encounter ATC at some point, its rarity makes it a difficult disease to manage effectively. Interestingly, about 40% of ATC cases have a *BRAF* V600E mutation. In 2018, the management of *BRAF* V600E-mutant ATC underwent a significant transformation with the FDA's approval of a combined treatment involving the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib.[95] This approval was based on an arm of the ROAR basket trial involving 23 patients and marked a significant milestone in the treatment of this rare and deadly cancer.[94] The development of BRAF/MEK inhibitors has significantly improved the prognosis for patients with *BRAF* V600-ATC, making molecular profiling essential for identifying eligible patients. This case serves as a model for developing and approving drugs for other rare cancers.

Erdheim-Chester disease/Langerhans cell histiocytosis

Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis (LCH) are two closely related clonal neoplasms originating from macrophage or dendritic cell lineages, and they are frequently associated with the *BRAF* V600 mutation.[96] The effectiveness of vemurafenib, a targeted inhibitor of the BRAF V600 kinase, has been well documented in patients with *BRAF* V600-mutant ECD and LCH through extensive clinical experience in France. This efficacy has been further validated in the VE-BASKET trial, a multi-histology basket study designed to evaluate vemurafenib in patients with various nonmelanoma cancers harboring the *BRAF* V600 mutation. The application of

vemurafenib in treating patients with *BRAF* V600-mutant ECD and LCH has shown significant and sustained antitumor effects. In the VE-BASKET trial, 85% of patients with ECD exhibited a confirmed ORR of 54.5% based on RECIST criteria, while the unconfirmed ORR reached 100% according to fluorodesoxyglucose-PET/CT scans.[96] Given that over half of patients with ECD and/or LCH carry the *BRAF* V600 mutation, these results have redefined the therapeutic approach for a substantial number of individuals with these rare diseases. The FDA has recognized the long-term, clinically meaningful benefits of vemurafenib in this context, leading to its approval for patients with *BRAF* V600-mutant ECD. Consequently, vemurafenib is now considered a viable and promising standard of care for these conditions.[96] The ideal length of vemurafenib therapy in ECD is still unknown. Untreated ECD, although histologically "benign," causes chronic bone pain, endocrine and renal dysfunction, and profound fatigue. BRAF inhibition rapidly relieves bone pain, normalizes inflammatory markers, and restores mobility within weeks. In published series, all responders remained in clinical and metabolic remission on doses below the melanoma standard (960 mg twice a day), with follow-up to 48 months. Discontinuation, however, led to relapse in most patients within $\leq$6 months, signaled by rising C-reactive protein and increased maximum standardized uptake value; retreatment uniformly regained control. These observations argue for trials of lower-dose maintenance or intermittent schedules guided by PET-CT and biomarkers. Benefits must be weighed against common toxicities, such as rash, photosensitivity, arthralgia, and secondary cutaneous carcinomas, that can erode long-term quality-of-life gains.[97]

Cholangiocarcinoma

Cholangiocarcinoma is a rare and aggressive tumor of the biliary tract. The standard first-line treatment for unresectable advanced cholangiocarcinoma is gemcitabine with cisplatin and durvalumab, based on the results of the TOPAZ-1 trial that showed that the addition of durvalumab to gemcitabine and cisplatin resulted in a modest improvement in survival compared to chemotherapy alone (median, 12.8 vs. 11.5 months).[98] Biliary tract carcinomas, especially intrahepatic cholangiocarcinomas, have multiple molecular alterations, with high potential for targeted therapies.[99,100] In a series of 454 biliary tract cancers, approximately 30.5% of them contained potentially actionable molecular alterations, 39% for intrahepatic cholangiocarcinoma.[101] *FGFR2* gene alterations are implicated in the development of cholangiocarcinoma, with ~9%–16% of such tumors exhibiting *FGFR2* alterations.[102] Pemigatinib (inhibitor of FGFRs 1–3) was tested in the FIGHT trial, an open-label, single-arm, phase 2 trial with three cohorts: *FGFR2* fusions or rearrangements, other *FGFR* alterations, or no *FGFR* alterations.[103] After a median follow-up of 17.8 months, 38 out of 105 patients (36%) with *FGFR2* fusions or rearrangements showed an objective response, with three complete responses. Futibatinib, an FGFR1–4 inhibitor, was evaluated in the second line in FOENIX-CCA2, an open-label, phase 2 trial in patients with intrahepatic cholangiocarcinoma harboring *FGFR2* rearrangements. At a median follow-up of 17 months, the median OS was 22 months.[104,105] In 2022, the FDA approved both pemigatinib and futibatinib for *FGFR2*-rearranged cholangiocarcinoma. *NTRK* rearrangement is present in ~3.6% of intrahepatic cholangiocarcinoma.[106] Larotrectinib and entrectinib have been tested in basket trials with encouraging results, allowing agnostic use of these molecules.[107,108] *BRAF* mutations are reported in ~5% of cholangiocarcinomas. Dabrafenib and trametinib have been tested in a phase 2, open-label ROAR basket trial with an ORR of over 50% and were initially added to the NCCN guidelines and are now approved in a tissue-agnostic manner across all tumors harboring *BRAF* V600 alterations, including cholangiocarcinoma.[109] *HER2* amplification or overexpression is present in up to 20% of cholangiocarcinomas.[110] Trastuzumab and pertuzumab have been tested in a basket trial,[111] and trastuzumab-deruxtecan was evaluated in a single-arm, phase 2 trial. It showed promising results.[112] In 2021, the FDA approved ivosidenib for treating adult patients with unresectable locally advanced or metastatic *IDH1*-mutated cholangiocarcinoma with disease progression after one to two prior lines of systemic therapy for advanced disease. The approval was based on data from study AG120-C-005 (ClarIDHy), a double-blind, placebo-controlled trial that randomly allocated (2:1) patients to receive either ivosidenib or placebo. The hazard ratio for PFS was 0.37 (95% CI 0.25, 0.54, $p < 0.0001$). Combined, cholangiocarcinoma can now be segmented into multiple molecular subsets with pharmacologically tractable alterations.

HCL

HCL is a rare leukemia characterized by an indolent course, splenomegaly, and progressive pancytopenia, generally without lymphadenopathy. The bone marrow, liver, and spleen are infiltrated by leukemic B cells with abundant cytoplasm, hairy-looking projections, and unique immunophenotypic features. Tartrate-resistant acid phosphatase (TRAP) is an essential, iron-binding protein found in the cytoplasmic granules of the leukemic cells of HCL; TRAP positivity can help distinguish HCL from other types of B cell malignancies.

The *BRAF* V600E mutation is a disease-defining molecular event in HCL. It is found in virtually 100% of patients.[113] Vemurafenib (a BRAF inhibitor) is highly effective, with a 96%–100% response rate after a short course (8–12 weeks) of therapy.[114,115] Given that combination BRAF+MEK therapy is the standard of care for other *BRAF* V600 mutations and that vemurafenib is often paired with rituximab, there are supporting data for the use of the BRAF+MEK inhibitor combination in HCL as well. Dabrafenib plus trametinib has shown durable responses and a manageable safety profile, consistent with observations in other conditions.[116] Therefore, this combination should be considered as a rituximab-free therapeutic option for patients with relapsed or refractory *BRAF* V600E mutation-positive HCL. Hence, HCL represents one of the most striking examples of an association between a characteristic molecular alteration and an effective matched targeted therapy (Figure 2).

TUMOR-AGNOSTIC REGULATORY APPROVALS: A PARADIGM SHIFT OF SPECIAL IMPORTANCE FOR RARE TUMORS

Since 2017, the landscape of cancer treatment has witnessed a transformation with the advent of tumor-agnostic therapies.

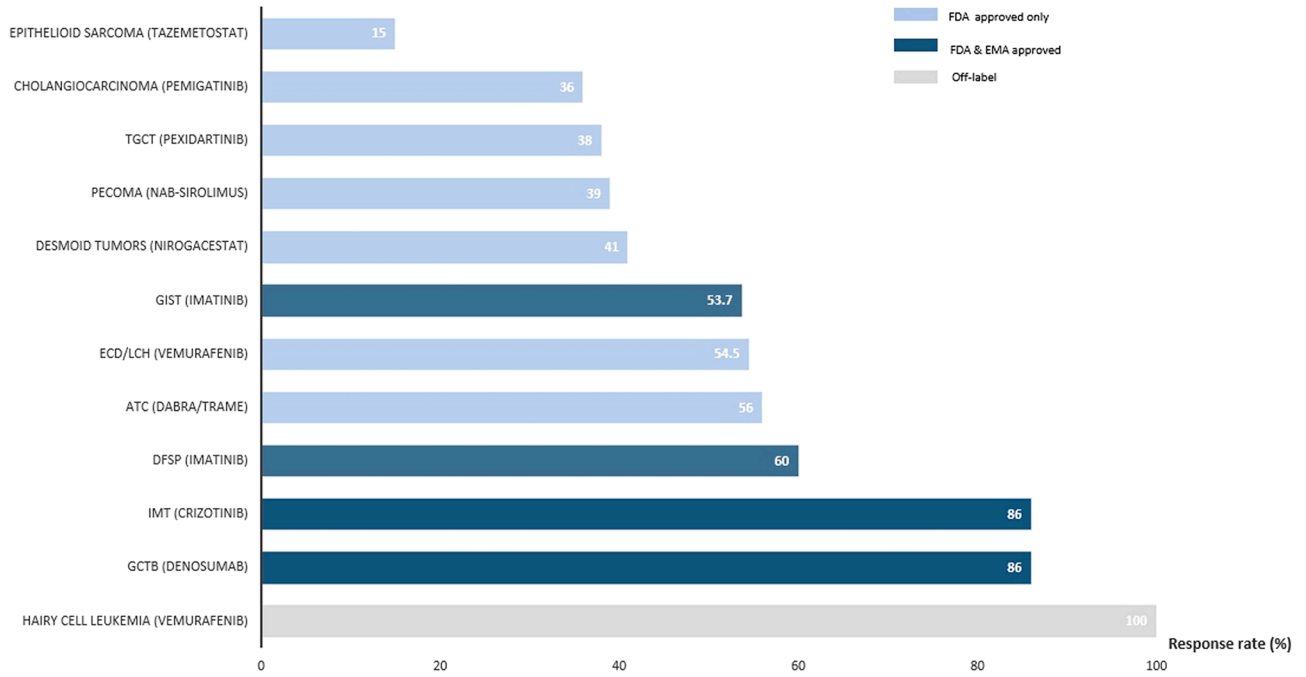

Figure 2. Objective response rates of targeted therapies in rare tumors and their FDA/EMA approval status

Traditionally, cancer treatments have been approved based on the specific site or organ where the cancer originates. However, tumor-agnostic therapies challenge this convention by targeting tumors based on their molecular characteristics rather than their location in the body. This paradigm shift has been facilitated by breathtaking advances in genomic research and personalized medicine, enabling oncologists to tailor treatments more precisely to individual patients.

The importance of the paradigm shift to tumor-agnostic therapies cannot be overemphasized vis-à-vis its importance for rare cancers.[19] Many molecular alterations occur in 0.1%–5% of tumors. Since rare tumors are commonly defined as <6 cases per 100,000 people, this means that the molecular alterations would quite literally be found in ~1 in a million people. Hence, performing clinical trials in a molecularly defined 1-in-a-million subset of each of the ~200 rare tumor types is not possible. More importantly, since the molecular alteration is the driver and high response rates with matched therapy are found regardless of tumor of origin, tissue-agnostic therapies deliver highly active treatments to patients suffering from rare malignancies, an underserved population[18–27] (Table 1).

Tumor-agnostic therapies are a breakthrough for rare cancers: they turn ultra-low-prevalence drivers into actionable targets across histologies and open a path to treatment when conventional trials are impossible. However, not every biomarker behaves in a truly agnostic way. Signals such as MSI-H/dMMR and *NTRK* fusions give high, durable responses across many tumor types; others, most notably tumor mutational burden (TMB)-high (≥10 mutations [mut]/Mb), show uneven benefit, shaped by tumor-specific biology, non-interchangeable assays, and co-drivers that dampen response.[117] Agnostic labels are best read as permissive access, not directives to treat: the strongest cases combine biological plausibility with robust, durable activity across several histologies.

Another practical challenge lies in biomarker heterogeneity. Genomic and non-genomic markers vary in interpretability and measurement: many findings in rare cancers remain variants of uncertain significance despite ACMG/AMP and ESCAT frameworks[118,119]; cross-laboratory concordance is imperfect. Several agnostic biomarkers are assay-dependent, TMB shifts with panel size and filters, and homologous recombination deficiency (HRD) readouts (genomic instability scores, loss-of-heterozygosity [LOH] cutoffs, and signature-based probabilities) are not interchangeable or uniformly valid across tumor types.[120,121] Emerging genome-level features (mutational signatures and chromothripsis) and protein/phosphoprotein markers add promise but lack standardization and prospective validation.[122] Practical guardrails help preserve the value of agnostic strategies for rare tumors: disclose platform and cutoffs in reports, prefer tumor-type-specific thresholds, route choices through molecular tumor boards (MTBs), and contribute outcomes to real-world registries so that evidence and harmonization improve over time.[123,124]

PLATFORM CLINICAL TRIALS AND INITIATIVES FOR RARE CANCERS

A broad ecosystem of precision-oncology platforms now targets rare cancers across every age group and continent. These platforms use shared control arms, adaptive baskets or umbrella cohorts, and central molecular boards to match patients with targeted or immuno-oncology agents, proving that even

Table 2. Platform clinical trials and initiatives for rare cancers

Year	Initiative	Lead (country/region)	Phase and design	Patients enrolled	Key results
Adult and all-age platforms					
2011	MOSCATO-01[125]	France	prospective, single-arm "genome-driven" basket; comprehensive NGS ± RNA; matched off-label therapy	1,035 sequenced; 49 received matched drug; included CUP, STS, NETs, rare entities of common tumors	33% achieved PFS ratio >1.3 vs. prior line; first European proof that molecular matching can improve outcomes across heterogeneous (often rare) tumors
2013	MASTER[126]	Germany	prospective registry with whole-genome/-transcriptome sequencing; central MTB issues treatment recommendations	1,311 profiled; 75% rare tumors; included STS and NETs	evidence-based targeted therapy recommended in 88%; those treated per MTB advice had significantly higher ORR and DCR vs. prior therapy
2015	NCI-MATCH[127]	US	phase 2 umbrella/basket; 38 genotype-guided arms	≈6,000 screened; 1,593 assigned to arms; included STS and NETs	feasibility proved; several 7/27 substudies met pre-specified ORR benchmarks
2016	MoST[128]	Australia	adaptive basket (panel screening, signal-seeking sub-trials)	8,303 screened; 1,176 entered matched therapeutic cohorts; 79% rare tumors; included CNS tumors, STS	matched therapy more than doubled expected survival in biomarker-positive patients
2016	DRUP[129]	the Netherlands	non-randomized signal-finding basket (off-label targeted/IO)	500 enrolled (164 patients with rare cancer); included cholangiocarcinomas, CNS tumors, NETs	clinical-benefit rate 33%; flexible cohort expansion informed Dutch reimbursement decisions
2017	SWOG DART[130]	US	phase 2 basket, nivolumab + ipilimumab	798 patients; included NETs and NENs, cholangiocarcinoma, gynecologic rare cancers, desmoid tumors, CUP, GISTs	durable responses in metaplastic breast (ORR $\geq$ 30%), angiosarcoma, NET NCCN guideline changes
2017	MASTER Key[131]	Japan	prospective registry + parallel phase 2 sub-trials under one protocol	>4,000 registered by June 2024; included CUP, rare subtypes of common cancers, STS, NETs, CNS tumors	ORR in matched vs. non-matched therapy: 40% vs. 9.8%; median DoR 165 vs. 84 days
2021	BOUQUET (ENGOT-GYN2)[132]	EU/US	multi-cohort, phase 2 umbrella	target ≈ 280; interim > 100; population: rare ovarian subtypes	MEK-inhibitor low-grade serous cohort: ORR 33%
2023	DETERMINE[133]	UK	phase 2 master protocol repurposing targeted drugs off label	goal: 650; recruiting	–
2024	RATIONALE[134]	Germany	randomized platform: molecular-guided therapy vs. standard in rare tumors	target: 750; opening 2025	–
2024	ProFiLER-02[135]	EU consortium	observational study comparing 50- vs. 500-gene panels	10,000 tumors analyzed; included sarcomas, CNS tumors, CUP, rare subtypes of common tumors	larger panel doubled the proportion of patients with rare tumors eligible for trials

(*Continued on next page*)

Table 2. *Continued*

Year	Initiative	Lead (country/region)	Phase and design	Patients enrolled	Key results
Pediatric platforms					
2015	INFORM[136]	EU	multinational registry with multiomics and central MTB	1,051 profiled (75% rare); included CNS tumors, sarcomas, CUP, rare epithelial cancers	targeted therapy recommendation in 88%; those treated per MTB had superior disease control
2016	MAPPYACTS (ClinicalTrials.gov: NCT02613962)	EU	prospective molecular-profiling trial feeding into early-phase baskets	787 enrolled; 107 received matched therapy; included CNS tumors, sarcomas, rare epithelial cancers	ORR 17% overall; 38% when alteration "ready for routine use"
2016	AcSé-ESMART (ClinicalTrials.gov: NCT02813135)	EU	adaptive phase 1-2, multi-arm basket; first-in-child combos	>150 treated across ≥10 arms; included CNS tumors, sarcomas, rare epithelial cancers	early cohorts (e.g., olaparib + temozolomide in DNA-repair tumors) reported durable CRs
2017	Pediatric MATCH[137]	US	master protocol with 10-plus genotype-matched phase 2 arms	1,371 screened; 414 assigned (as of 2022); included CNS tumors, sarcomas, rare epithelial cancers, ECD/LCH, non-Hodgkin's lymphomas	feasibility proven nationwide; objective responses in ALK, BRAF, FGFR arms
2017	ZERO Childhood Cancer[138]	Australia	national precision program with MTB-guided therapy	384 high-risk patients analyzed; included CNS tumors, sarcomas, rare epithelial cancers, hematologic neoplasms, ECD/LCH	guided therapy: PFS 26% vs. 12% (standard); 55% achieved CR/PR or ≥6-month SD
2020	MCI (Molecular Characterization Initiative)[139]	US	centralized WGS/RNA + MTB for newly diagnosed pediatric CNS tumors	>1,400 cases sequenced (2024); included CNS tumors and sarcomas	real-time genomic report <14 days; guides front-line therapy and trial referral

IO, immunotherapy; MTB, molecular tumor boards; DCR, disease control rate; NETs, neuroendocrine tumors; NENs, neuroendocrine neoplasms; STS, soft-tissue sarcoma; CNS, central nervous system; CUP, cancer of unknown primary; ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; NGS, next-generation sequencing; WGS, whole-genome sequencing; DoR, duration of response; CR, complete response; SD, stable disease

ultra-rare malignancies can be studied efficiently and treated with biology-driven therapies (Table 2).

CONCLUSIONS AND FUTURE DIRECTIONS: FROM MOLECULARLY DEFINED DISEASE SUBSETS TO *N*-OF-1

The precision-oncology era has brought hope to diseases once unresponsive to systemic therapy while forcing us to rethink trial design and therapeutic strategy. Basket and platform studies, capable of enrolling patients across tumor types into a single protocol, have become indispensable for generating robust evidence in the small cohorts that typify incidence-defined rare and ultra-rare cancers (≤6 cases per 100,000, or ≤1 per 1,000,000 for some sarcomas). Decision-support algorithms and MTBs now guide treatment in these settings, and international consortia provide the critical mass needed for translational research and prospective trials.

Rare cancers, by definition, are individually uncommon but, taken together, comprise >20% of the total cancer burden. Moreover, there are now many types of "rare": (1) tumors that are rare based on traditional histology/anatomic classifications (and which often have a unifying molecular driver) (e.g., HCL [*BRAF* V600E found in ∼100% of patients]); (2) infrequent subsets of common tumors, with NSCLC being the poster child (∼70% of NSCLCs presently showing molecular subgroups including, but not limited to, *RET*, *MET*, *EGFR*, *HER2*, *BRAF*, and *ALK* altered); and (3) molecularly defined, tumor-agnostic cancers, now with multiple FDA approvals (e.g., *NTRK* fusions, *RET* altered, HER2 3+ expressing, *BRAF* V600E, and dMMR/MSI-H) (Figure 3). Concurrently, molecularly defined subsets within common tumors, for instance, *ALK*-rearranged or *RET*-mutant lung adenocarcinoma, occupy a different but complementary landscape. Although numerically small, these cohorts profit from the diagnostic pathways, natural history data, and modeling platforms of their parent disease. The knowledge generated in these biomarker-selected niches is beginning to feed back into the management of historically rare cancers. A telling example comes from mesenchymal tumors harboring *NTRK* or *ALK* fusions. Larotrectinib was developed in TRK-fusion-positive carcinomas, yet its activity in a handful of infantile fibrosarcomas secured these ultra-rare sarcomas a place in the drug's first-in-class histology-agnostic approval. Likewise,

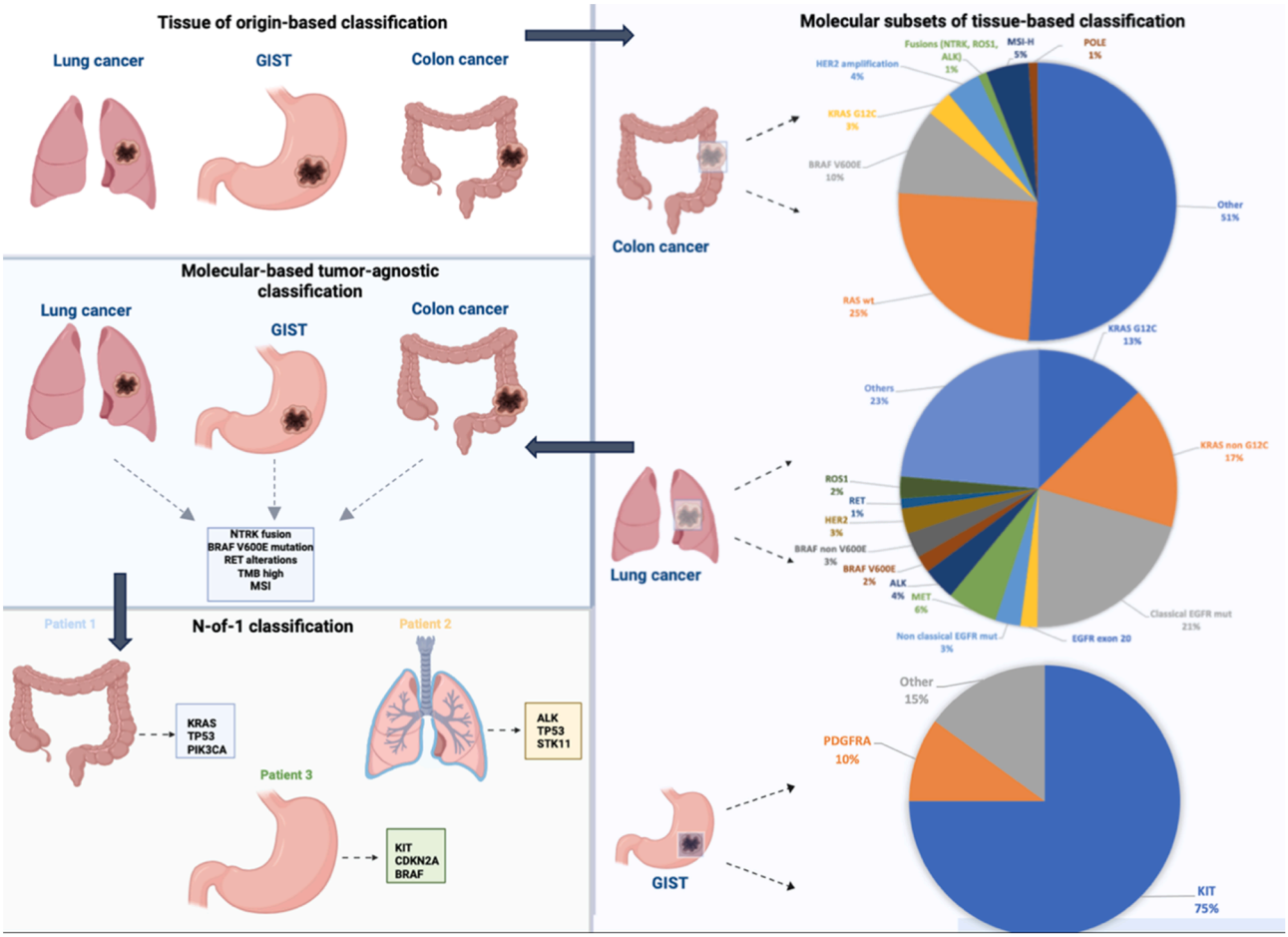

Figure 3. An evolving classification in cancer drives precision oncology

The traditional approach of classifying patients by histology and using the same treatment for large, unselected groups has been practical but is limited by biological variation. Over the past decade, targeted therapies matched to specific molecular alterations have emerged, proving successful in rare cancers, such as imatinib for GISTs, and common cancers, such as EGFR, ALK, and MET inhibitors for NSCLC. *n*-of-1 trials take this further by tailoring treatments to a patient's unique molecular profile, offering personalized care and accelerating drug development. The percentages of molecular alterations in non-small cell lung cancer were derived from previous work conducted by Friedlaender et al.[140] *RET*, rearranged during transfection; HER2, human epidermal growth factor receptor 2; *BRAF*, B-raf murine sarcoma viral homolog B; *ROS1*, ROS proto-oncogene 1; *MET*, c-Met; *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma; *STK11*, serine/threonine protein kinase 11; *NTRK*, neurotrophic tyrosine receptor kinase.

crizotinib, optimized in *ALK*-rearranged NSCLC, was rapidly repurposed for IMTs, yielding response rates comparable to those seen in the lung and sparing patients the impossibility of a dedicated randomized trial. Such cross-pollination shows the practical value of a layered trial ecosystem that welcomes both incidence-defined rarities and biomarker-defined subgroups under a single adaptive umbrella.

While these molecular reclassifications provide the scientific foundation for precision oncology, translation into practice requires innovative trial designs that can accommodate rare disease constraints. Platform trials have emerged as a cornerstone for rare cancer research, successfully demonstrating efficiency gains through simultaneous evaluation of multiple treatments and adaptive design capabilities. However, real-world implementation reveals substantial challenges that must be acknowledged. The NCI-MATCH trial depicts both promise and limitations: while it registered 6,391 patients, only 17.8% of patients were assigned to treatment arms due to actionable alterations and additional exclusion criteria.[141] Operational complexities include unprecedented coordination requirements across 1,000+ accrual sites, substantial infrastructure investments requiring alternative funding mechanisms beyond traditional approaches, and statistical challenges, including biomarker-driven patient exclusions of NCI-MATCH patients with targetable alterations that were excluded due to co-occurring resistance-driving mutations.[142] Furthermore, regulatory frameworks continue evolving, with the FDA master protocol partially differing from the EMA's platform trial approach, creating international harmonization problems, which necessitate enhanced collaboration opportunities.[143]

Platform trials solve several rare-cancer research barriers yet add operational complexity. Deep molecular profiling also

Box 2. *n*-of-1 trials

An *n*-of-1 trial prospectively tests an investigational therapy in a single patient who serves as their own control, using real-time pharmacokinetic or biomarker-guided dose escalation to reach an active, tolerable exposure within days. The design is emerging because targeted and tissue-agnostic drugs now outpace classical 3+3 phase 1 pipelines, and rare genomic alterations splinter recruitment for cohort-based studies. Well-documented cases, such as selitrectinib rescuing TRK-inhibitor resistance, selpercatinib establishing the eventual phase 1 dose for RET cancers, bespoke RET + MET or EGFR + RET inhibitor doublets, and pediatric glioma responses to lorlatinib, show that single-patient protocols can reveal efficacy, dose, safety, and resistance mechanisms months before multicenter trials are complete.[151] In the US, a single-patient investigational new drug application (IND) aligned with real-time oncology review can activate such studies within hours; the EU Clinical Trials Regulation and Japan's compassionate-use pathway offer slower analogs. Aggregating raw data across *n*-of-1 studies with hierarchical Bayesian models can generate class-level dose-response estimates and feed "digital-twin" libraries that match future patients. Key obstacles remain, including protocol heterogeneity, publication bias against negative cases, and drug-supply or sequencing gaps in low-resource settings, but harmonized templates, open registries, and equity-focused logistics (e.g., WHO-UICC ATOM) could transform *n*-of-1 trials from boutique exceptions into a scalable, learning platform that accelerates drug development and delivers personalized benefit in real time.

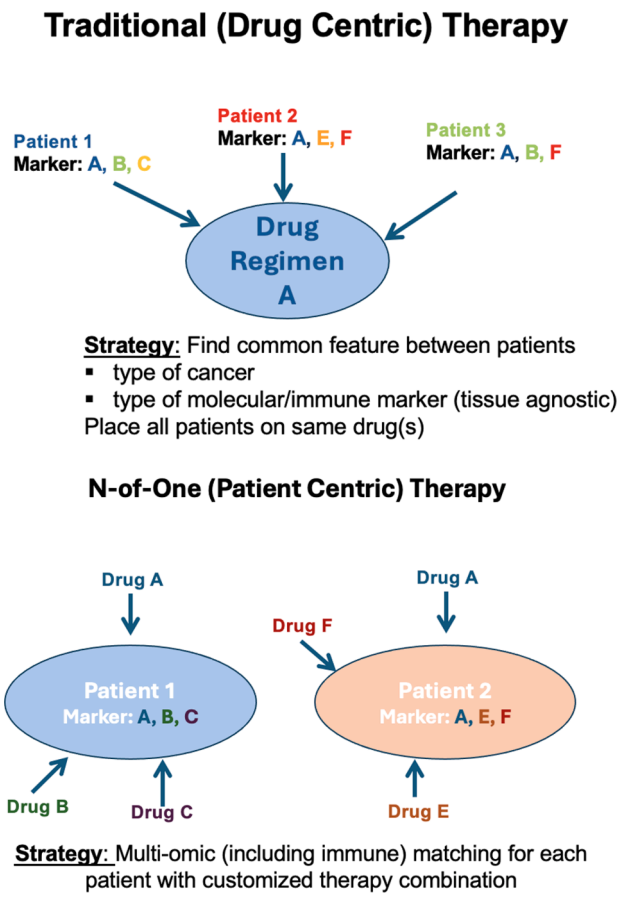

Figure 4. The paradigm shifts in cancer treatment

In rare tumors, limited patient recruitment hinders the conduct of randomized studies. *n*-of-1 trials offer a solution by accelerating drug development through personalized, interpatient dose escalation, bypassing standard trial delays. These trials allow patients to receive different treatments or placebos in sequence, enabling comparisons within the same patient over time. Real-time pharmacokinetic-guided adjustments further speed up the process, contrasting with traditional trials that rely on toxicity observations, often causing delays. The figure was adapted from Subbiah and Kurzrock.[156]

exposes a more fundamental reality: metastatic cancers are highly heterogeneous and often patient specific. In that context, single-patient evidence has value but must be handled carefully; well-documented case reports can show feasibility, dosing, and safety, yet they remain observational and hypothesis generating. A prospective *n*-of-1 trial turns that anecdote into a prespecified experiment in a single patient (Box 2). Given the high levels of tumor heterogeneity between patients, personalized *n*-of-1 combination therapy emerges as the next step (Figure 4). Tumors are not only rare or ultra-rare but also frequently one of a kind. Rather than approving fixed drug pairs for fixed diseases, the field may need to approve algorithms that tailor combinations to each patient and tumor. Master registries and real-world data can supply the large, clinically rich datasets required to refine these algorithms and to drive the precision (r)evolution.[144] Early *n*-of-1 programs, using genomic and transcriptomic markers, starting at low doses, and adapting intra-patient dosing to minimize toxicity, have already shown feasibility and are associated with better outcomes, supporting this pathway from disciplined single-patient testing to broader practice[145–150] (Figure 3). Future studies may build on this experience and leverage multiomic interrogation, real-world data, and machine learning/artificial intelligence to optimize *n*-of-1 biomarker-matched precision combination drug treatments.

While *n*-of-1 trials offer compelling theoretical advantages for precision medicine individualization, their implementation faces significant evidence-based difficulties that warrant critical evaluation. Study limitations restrict *n*-of-1 trials mainly to slowly growing cancers, excluding aggressive cancer entities that progress too quickly for patients to try multiple treatments safely.[151] The challenges due to evidence generation include weak statistical power from single-patient studies and unclear regulatory acceptance, as traditional clinical trial systems require large patient groups rather than individual patient data. Implementation barriers include the need for specialized facilities, lack of healthcare provider training, and unequal access, as *N*-of-1 trials are mainly available at large medical centers, potentially excluding patients in rural or underserved areas.[152]

The optimal future likely involves strategic integration of both approaches, recognizing their complementary roles and distinct limitations. Platform trials will continue serving as the foundation for generating robust evidence in molecularly defined rare cancer cohorts, while *n*-of-1 trials may prove most valuable for patients with ultra-rare alterations or those who have exhausted standard options within existing platforms. Early evidence supports this integrated approach, as demonstrated

Box 3. The place of off-label treatments in rare tumors

Regulators (FDA, EMA, Swissmedic, and PMDA) guarantee drug quality, safety, and efficacy, yet the system strains under the economics of ultra-orphan indications. Of the 33 onco-orphan drugs cleared by the FDA between 2018 and 2024, 21% were never filed in Europe, and those that were faced a median 10-month FDA-to-EMA lag, followed by 6–18 additional months of national HTA debate[157,158]. Tarlatamab illustrates the gap: FDA approved for extensive-stage small-cell lung cancer in May 2024, it remains under EMA review a year later, with only a conditional MHRA license and no EU-5 pricing deal. When licensed options stall, clinicians understandably turn to off-label or repurposed drugs, roughly 30% of systemic oncology use overall and far higher in biomarker-defined niches.[28] The US cushions this practice through the NCCN Compendium, whose level 2A recommendations trigger Medicare and most private reimbursement; more than 60% of these uses later gain formal FDA label expansion or phase 3 confirmation.[28] Europe, by contrast, offers a patchwork of early-access routes (France's ATU, the UK's EAMS, and Germany's Einzelantrag), leaving coverage uneven and many central and eastern countries without a mechanism at al.[159] Still, repurposing is not risk free. Significant genotype-directed trials show stark heterogeneity: response rates exceeded 30% in I-PREDICT and MOSCATO when potent inhibitors targeted high-rank alterations, yet the SHIVA trial, which matched weaker targets to available drugs, failed to improve and, in some arms, worsened outcomes.[160] These data underscore that off-label success hinges on rigorous variant interpretation (e.g., ESCAT tier I/II) and that reimbursement should be tied to real-world outcome reporting so that ineffective matches can be quickly de-implemented. Whether a positive rare tumor trial becomes bedside reality depends on three linked hurdles: regulatory divergence and delay, HTA price negotiation, and fragmented off-label frameworks. Pragmatic fixes include parallel FDA-EMA scientific advice for orphan drugs, joint HTA pilots, and registry-anchored reimbursement schemes that turn every off-label dispense into curated evidence rather than a last-resort gamble.

by Boston Children's Hospital's custom antisense oligonucleotide program, which led to the FDA's 2024 procedural guidance, and international initiatives, such as Project Orbis, that show high approval rates across partner countries for oncology collaborations.[153,154]

Transitioning from an innovative trial design to a scalable clinical practice will require ongoing collaboration among researchers, regulators, industry representatives, and patient advocates. Patient perspective, advocacy, and shared decision-making are essential to operationalize both platform and *n*-of-1 strategies in rare-tumor care. European reference networks (e.g., EURACAN) speed expert referral and provide multilingual materials that prepare families for consultations.[155] MTBs can issue plain-language summaries; in some centers, precision-oncology consultations review MTB results, clinical trial opportunities, and early-access/off-label pathways with patients (Box 3). Patient navigators and advocacy groups support logistics, financial counseling, and reimbursement. Finally, contributing outcomes to real-world registries turns individual experiences, especially from agnostic labels or *N*-of-1 designs, into shared evidence that informs future care. Success should be evaluated not only by the degree of treatment personalization achieved but also by the equitable delivery of these treatments across diverse healthcare settings.

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