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Controversy

If it's a target, it's a pan-cancer target: Tissue is not the issue

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ABSTRACT

Cancer is traditionally diagnosed and treated on the basis of its organ of origin (e.g., lung or colon cancer). However, organ-of-origin diagnostics does not reveal the underlying oncogenic drivers. Fortunately, molecular diagnostics have advanced at a breathtaking pace, and it is increasingly apparent that cancer is a disease of the genome. Hence, we now have multiple genomic biomarker-based, tissue-agnostic Food and Drug Administration approvals for both gene- and immune-targeted therapies (larotrectinib/entrectinib, for *NTRK* fusions; selpercatinib, *RET* fusions; dabrafenib plus trametinib, $BRAF^{V600E}$ mutations; pembrolizumab/dostarlimab, microsatellite instability; and pembrolizumab for high tumor mutational burden; pemigatinib is also approved for *FGFR1*-rearranged myeloid/lymphoid neoplasms). There are emerging targets as well, including but not limited to *ALK*, *BRCA* and/or homologous repair deficiency, *ERBB2 (HER2), IDH1/2, KIT,* $KRAS^{G12C}$, *NRG1,* and *VHL.* Many tissue-agnostic approvals center on rare/ultra-rare biomarkers (often < 1 % of cancers), necessitating screening hundreds of tumors to find a single one harboring the cognate molecular alteration. Approval has generally been based on small single-arm studies (<30–100 patients) with high response rates (>30 % to > 75 %) of remarkable durability. Because of biomarker rarity, single-gene testing is not practical; next generation sequencing of hundreds of genes must be performed to obtain timely answers. Resistance to biomarker-driven therapeutics is often due to secondary mutations or co-driver gene defects; studies are now addressing the need for customized drug combinations matched to the complex molecular alteration portfolio in each tumor. Future investigation should expand tissue-agnostic therapeutics to encompass both hematologic and solid malignancies and include biomarkers beyond those that are DNA-based.

Introduction

Historically, cancer has been classified and treated on the basis of its organ of origin (e.g., breast or colon or lung cancer), which is determined by light microscopy. However, light microscopy does not uncover the factors that drive tumor formation and progression. Understanding tumor drivers requires molecular technology, which has fortunately advanced at a remarkable rate over the last two decades. As a result, there are now multiple tissue-agnostic Food and Drug Administration (FDA) approvals for patients with cancer (Fig. 1) [1–18] Tissue-agnostic approvals imply that the organ of origin is not considered germane for the FDA approval. In other words, a treatment is approved for its ability to target a specific molecular abnormality, and all patients with that abnormality, regardless of the organ of origin of their tumor, can receive that treatment.[19,20] These approvals have been enabled by the advent of molecular genomic testing and, more recently, clinical-grade next-generation sequencing (NGS), which can simultaneously probe tumors for thousands of possible abnormalities in any one of hundreds of

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cancer-causing genes. In addition to established tissue-agnostic approvals, multiple new gene anomalies are emerging as potential tissue-agnostic targets. Importantly, we posit that all genomic markers may be candidate tumor-agnostic biomarkers—tissue is not the issue.

The molecular microscope and the reclassification of cancer

Although the light microscope was invented over 400 years ago, and the hematoxylin and eosin stain, which is the gold standard for histologic identification, was developed about 150 years ago, the human genome was only first sequenced in 2001.[21–24]. Still, oncologists, pathologists, and researchers have embraced the compelling evidence that cancer is a disease of the genome.

NGS is akin to a molecular microscope. Interrogation of cancers at a molecular level and their prosecution with gene-targeted therapies has led to the reclassification of cancer, which in turn has led to multiple regulatory authorizations that require a genomic biomarker.[19,20] While most of these approvals are still within the context of organ of origin, e.g. approval of ALK inhibitors for patients with non-small cell lung cancer (NSCLC) harboring *ALK* fusions [25,26], more recently, FDA approvals have shed the focus on organ of origin and have concentrated on genomic anomalies, giving rise to tissue-agnostic approvals. [1–18,27–29].

Tissue-agnostic approvals for gene- and immune-targeted therapies

Tissue-agnostic approvals are based on genomic biomarkers including mutations, fusions/rearrangements, and tumor mutational burden (TMB)/microsatellite instability. The approved agents encompass small molecule inhibitors and antibodies. Both gene- and immune-targeted drugs have attained tissue-agnostic approvals, and the approvals have been applied for solid cancers and for hematologic malignancies (Fig. 1).

In the solid tumor field, the tissue-agnostic FDA gene-targeted approvals are as follows: [1–18,27–29] TRK inhibitors larotrectinib and entrectinib for *NTRK* fusions; the RET inhibitor selpercatinib for *RET* fusions; and the BRAF inhibitor dabrafenib combined with the MEK inhibitor trametinib for *BRAF V600E* mutations. In the hematologic field, the FGFR inhibitor pemigatinib targets *FGFR1* rearrangement in myeloid lymphoid neoplasms. In the immunotherapy field, the anti-PD1 antibodies pembrolizumab and dostarlimab are each approved for solid tumors with microsatellite instability-high (MSI-H), and pembrolizumab is also approved for solid tumors with high TMB (≥10 mutations/mb). All these approvals are partial, as they include solid tumors but not hematologic malignancies or vice versa; moreover, in the case of *BRAF V600E*, colorectal cancer is excluded [1–21,27–29].

Tissue-agnostic FDA approvals have several key features: (i) they require a genomic biomarker for both gene-targeted therapy and for immunotherapy; (ii) they are established on the basis of single-arm studies with small numbers of patients (<30 to 100); (iii) the genomic biomarker may be rare or ultra-rare and hence hundreds of patients may need to be screened to find single cancers harboring the cognate anomaly; and (iv) response rates are high (>30 % to > 75 %) and benefit is remarkably durable.

The rarity of the genomic biomarkers that underly tissue-agnostic approvals is important. *RET* fusions appear in only 0.23 % of all cancers, and roughly 1–2 % of all patients with NSCLCs.[30–34] Similarly, *NTRK* fusions are discerned in only 0.31 % of adult tumors and in 0.34 % of pediatric tumors.[35] *BRAF V600E* alterations are seen in ~ 2.5 % of cancers.[36] Microsatellite instability is observed in about 4 % of cancers [37] and TMB ≥ 10 mutations/mb is found in 5 to 13 % of patients. [38,39].

The fact that these molecular biomarkers are rare or ultra-rare has important real-world implications. Notably, single gene tests are not practical in the clinic as the physician cannot possibly "guess" which gene test to order, and tissue is soon exhausted by running single tests. Furthermore, the patient's disease is generally progressing and there is no time to serially order tests. Fortunately, NGS is a comprehensive profiling technique that allows hundreds of cancer-causing genes to be tested at once, and returns results within 2–3 weeks, without using substantially more tissue than single tests. Both tumor tissue and blood can be evaluated by NGS.

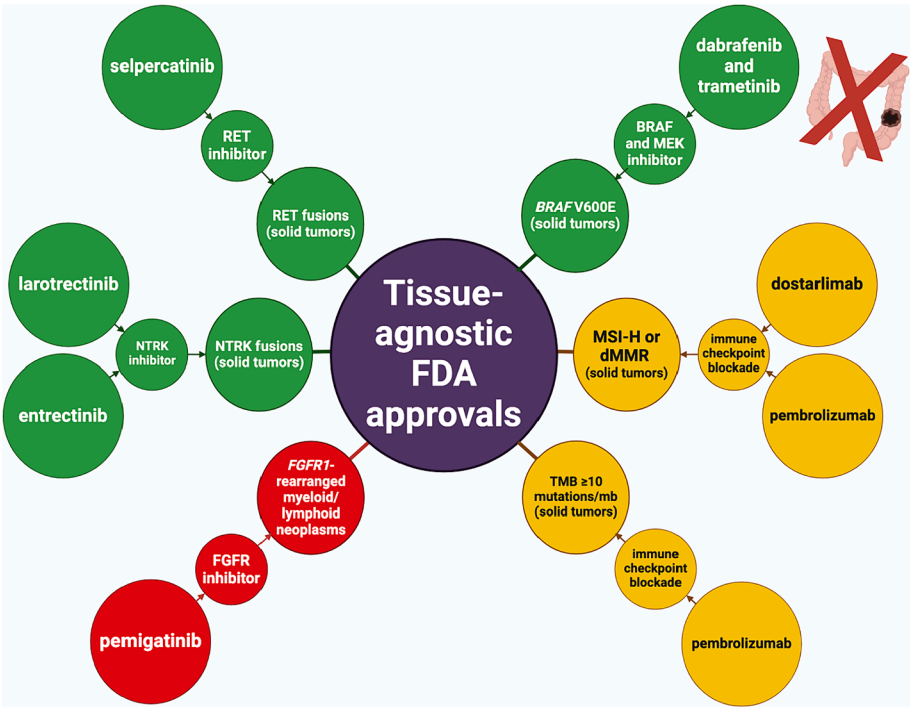

Fig. 1. Tissue-agnostic FDA approval. Figure Legend: This figure represents tissue-agnostic FDA-approvals. Colorectal cancer was excluded from the *BRAF V600E*-directed trametinib plus dabrafenib approval. Created with BioRender.com.

Emerging tissue-agnostic biomarker targets

There are multiple up-and-coming tissue-agnostic targets including but not limited to, *ALK, BRCA, ERBB2 (HER2), IDH1/2, KIT,* and *KRAS G12C, NRG,* and Von Hippel-Lindau *(VHL)* as well as homologous repair deficiency (HRD) (Table 1 and Fig. 2).[25,40–71] They can be effectively targeted by several types of medications: antibodies, antibody-drug conjugates and small molecule inhibitors. Each of these genes, when aberrant, can be impacted by one or more medications, and there are already approvals in distinct cancers bearing the cognate biomarker and/or robust clinical evidence for activity in diverse cancer types.

One notable example of an emerging tissue-agnostic target derives from the FDA approval of the hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor belzutifan for patients with germline *VHL* mutations; these mutations induce NF-κB activity through the accumulation of HIFα expression.[40] The belzutifan approval simultaneously included several different solid tumors (renal cell carcinoma, central nervous system hemangioblastomas, and pancreatic neuroendocrine tumors) in patients with germline *VHL* disease, with objective response rates (ORRs) ranging from 49 % to 85 %.[41,42].

There are multiple other biomarkers susceptible to inhibition by gene-targeting agents that are active across tissue types. For example, *ALK* genomic alterations are found in ~ 3.3 % of malignancies, though *ALK* fusions/rearrangements, which are especially vulnerable to effective targeting, are less common, occurring in ~ 0.5–0.8 % of cancers.[25] To date, multiple ALK inhibitors have been granted approval by the FDA for *ALK*-altered NSCLC treatment: first-generation inhibitors (crizotinib), second-generation (ceritinib, alectinib, and brigatinib) and third generation ALK inhibitors (lorlatinib). Moreover, ALK inhibitors have demonstrated activity in a range of solid and blood cancers and have been garnered FDA approval in inflammatory myofibroblastic tumors and in anaplastic large cell lymphomas. The approved ALK inhibitors yield ORRs between ~ 44 % to ~ 90 % across malignant solid and hematologic conditions.[25].

BRCA is a tumor suppressor gene and is one of a set of genes implicated in double-stranded DNA repair by homologous recombination. Testing for HRD is possible and is a functional way to detect the downstream effects of *BRCA* mutations (germline or somatic) as well as alterations in several other genes that are critical for DNA repair. The incidence of *BRCA1* or *BRCA2* germline mutations within the general population is low (~1 out of every 300 to 800 people.) While the risk of breast cancer development is the highest of the epithelial malignancies (between 40 % and 80 %), the chance of developing other cancers including ovarian, pancreatic, and prostate is also increased in patients carrying germline *BRCA1* and *BRCA2* mutations.[45] *BRCA* mutations may also be somatic. Tumors with defects in *BRCA* or elevated HRD are sensitive to platinum agents and to PARP inhibitors, with several of the latter approved: olaparib, rucaparib, niraparib, and talazoparib. These drugs are authorized for diverse cancers such as breast, ovarian, prostate and pancreatic cancer.[46].

ERBB2/HER2 is another target with ample data supporting cross-tumor activity. HER2 overexpression (mostly but not exclusively due

Table 1
Examples of Emerging Tissue-Agnostic Biomarker Targets and Medications [25,40–71].

Gene	Examples of drugs that target the alteration	Examples of tumors with FDA approvals or activity in clinical trials based on the cognate aberrant biomarker	Comment
ALK	Crizotinib, ceritinib alectinib, brigatinib, lorlatinib (all FDA approved)	Non-small cell lung cancer, inflammatory myofibroblastic tumors, and anaplastic large cell lymphomas (FDA approved; all with *ALK* fusions)	Most activity is for *ALK* fusions
BRCA (and homologous repair deficiency (HRD))	Olaparib, rucaparib, niraparib, talazoparib (all FDA approved) Platinums (FDA approved)	Breast, ovarian, prostate and pancreatic cancer (FDA approved, all with *BRCA* mutations)	Both *BRCA1* and *BRCA2* can manifest as somatic or germline mutationsHomologous repair deficiency (HRD high) is a functional consequence of mutations in *BRCA* and other DNA repair genes and sensitizes to PARP inhibitors or to platinum agents
ERBB2/HER2	Multiple drugs Tucatinib and trastuzumab deruxtecan have approvals outside of breast and gastric cancers (FDA approved drug)	Breast, non-small lung cancer, gastric, colorectal cancer (FDA approved, all with ERBB2/HER2 expression or *ERBB2/HER2* mutations depending on the indication)	The antibody-drug conjugate trastuzumab deruxtecan has shown activity across cancers with *ERBB2* expression.
IDH1 and *IDH2*	Ivosidenib and olutasidenib (IDH1 inhibitors) and enasidenib (IDH2 inhibitor) (FDA approved) Vorasidenib (IDH1 and IDH2 inhibitor) (clinical trial activity	Acute myeloid leukemia, myelodysplastic syndrome, cholangiocarcinoma (FDA approved indications, all with *IDH* mutations) Vorasidenib (gliomas) (*IDH*-mutant)	
KIT	Imatinib, avapritinib, ripretinib, sunitinib, regorafenib (FDA approved drug)	Gastrointestinal stromal tumors and systemic mastocytosis (FDA approved, tumors typically have *KIT* mutations)	
KRAS G12C	Sotorasib, adagrasib (FDA approved) Divarasib (clinical trial activity) Glecirasib (clinical trial activity)	FDA approvals for non-small cell lung cancer with KRAS *G12C* mutations Activity for divarasib seen across *KRAS G12C*-mutated solid cancers (clinical trial activity) Activity for glecirasib seen across *KRAS G12C*-mutated solid cancers (clinical trial activity)	
NRG1	Zenocutuzumab (Investigational antibody)	Multiple tumor types with *NRG1* fusions (clinical trial activity)	
VHL	Belzutifan (FDA approved)	*VHL*-mutated associated renal cell cancer, central nervous system hemangioblastomas and pancreatic neuroendocrine tumors (FDA approved)	FDA approval is for germline *VHL*-mutated diseaseBelzutifan is also FDA approved for renal cell carcinoma (no biomarker)

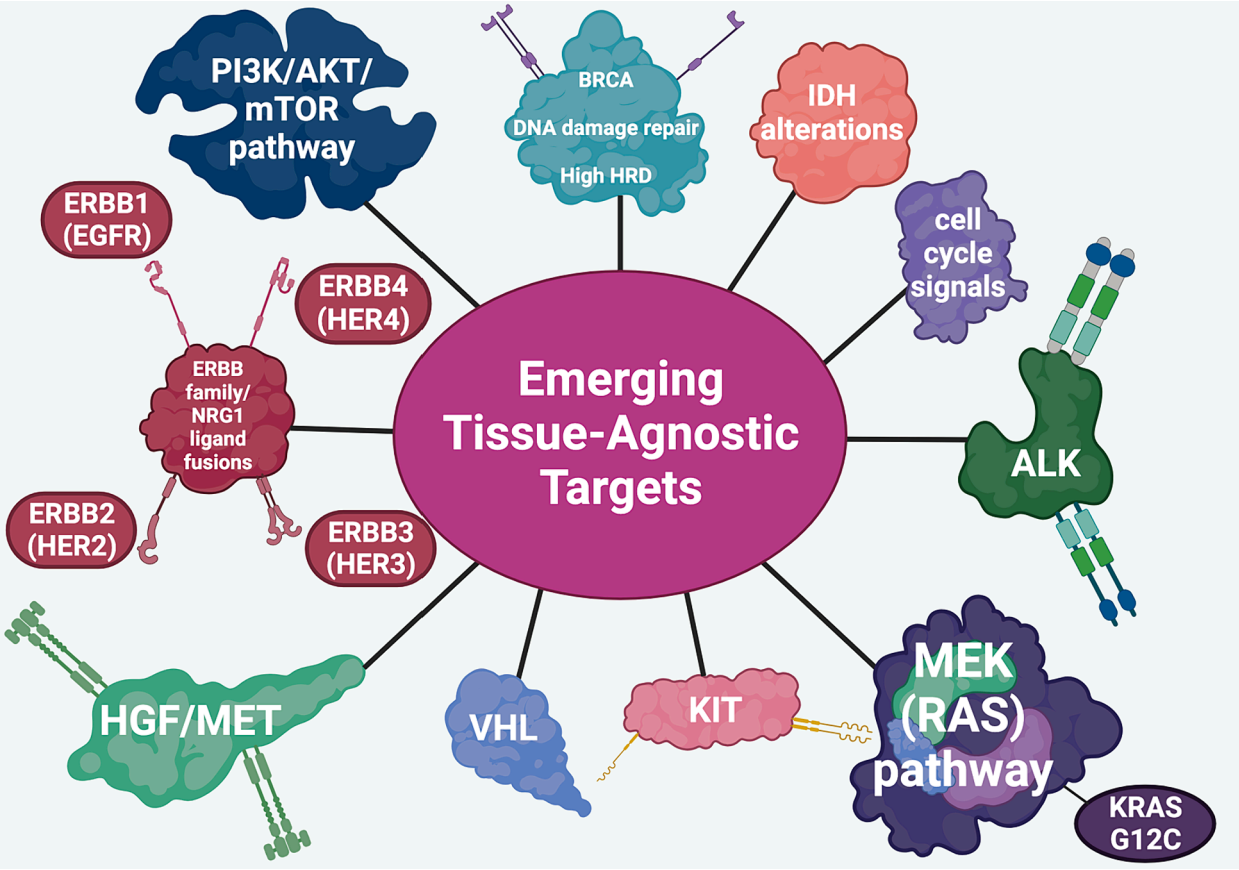

Fig. 2. Examples of emerging tissue-agnostic targets. Figure Legend: This figure represents multiple potential tissue-agnostic targets. Created with BioRender.com.

to *ERBB2* (HER2) amplification) is found in ~ 3 % of tumors.[47–50] Similarly, *ERBB2* mutations (which generally result in kinase enzyme overactivation rather than increased expression) also occur in ~ 3 % of cancers.[51,52] The antibody-drug conjugate trastuzumab deruxtecan has salutary effects in multiple tumor types that express HER2 (including low levels of HER2, i.e., <3 + by immunohistochemistry [IHC]) and tumors that have *ERBB2* (HER2) mutations.[53–55] Trastuzumab deruxtecan is approved for adults with advanced/metastatic HER2-positive breast cancer (including 1+/2 + HER2 IHC), NSCLC with *ERBB2* (*HER2*) mutations, and HER2-positive gastric or gastroesophageal junction adenocarcinoma.[56] The small molecule HER2 inhibitor tucatinib combined with the HER2-targeting antibody trastuzumab is also approved for *RAS* wild-type HER2-positive unresectable or metastatic colorectal cancer.[57].

On a related note, NRG1 binds to ERBB3/HER3 and ERBB4/HER4. ERBB3/HER3 lacks or has little intrinsic tyrosine kinase enzymatic activity; however, it often forms heterodimers with other ERBB/HER tyrosine kinases including ERBB2/HER3 and, in neoplastic cells, can stimulate oncogenic signaling. Activating *NRG1* fusions can be discerned in diverse malignancies, albeit at a very low rate – ~0.15–0.5 % – across cancers [58] Drugs targeting the consequences of *NRG1* fusions are currently under development. The HER2-HER3 bispecific antibody zenocutuzumab has received FDA fast-track designation; it docks on ERBB2/HER2, and then binds to and blocks the NRG1 fusion-ERBB3/HER3 interaction and ERBB3/HER3 heterodimerization with ERBB2/HER2. The ORR was 34 % and median duration of response of 9.1 months across multiple *NRG1* fusion-bearing solid tumors (e.g., NSCLC, pancreas cancer, breast cancer, cholangiocarcinoma).[59].

KIT is a tyrosine kinase receptor. Activating *KIT* mutations occur in ~ 3 % of cancers.[60] There are now multiple approved KIT inhibitors including imatinib, avapritinib, ripretinib, sunitinib, and regorafenib. These agents are approved for *KIT*-mutated disease such as gastrointestinal stromal tumors (GIST) and systemic mastocytosis.[63,64] In the case of GIST, which previously had response rates approaching zero for cytotoxic chemotherapy, KIT inhibitors matched to specific *KIT* mutations result in responses in the majority of patients, transforming the outlook for people afflicted with GIST.[64].

KRAS is an especially interesting target. Previously it was considered undruggable, but this has rapidly changed, with two specific KRAS G12C inhibitors (sotorasib and adagrasib) now FDA approved, and others in development for *KRAS G12C* and multiple other types of *KRAS* mutations.[61,62] *KRAS* alterations activate the MEK pathway. Multiple MEK pathway inhibitors are also approved and have some, albeit limited, activity in *KRAS*-altered cancers, in part perhaps because of the frequent co-occurrence of other driver genomic alterations that need to be co-targeted in order to observe anti-tumor activity.[65] *KRAS* is frequently aberrant in cancer. Amongst > 79,000 tumors, 17 % had *KRAS* mutations with 12 % being $KRAS^{G12C}$ (2 % of the total mutations).[66] The KRAS protein acts as a signaling GTPase, transitioning between active GTP-bound and inactive GDP-bound conformations. *KRAS* mutants hinder the guanine exchange cycle, leading to its detention in an active state that promotes oncogenic signals. As mentioned, both sotorasib and adagrasib are FDA approved for NSCLCs bearing *KRAS G12C* mutations, but activity across cancers can be seen for these drugs as well as the investigational agent divarasib and glecirasib.[67,72] Recently it was also reported that a patient with *NRAS G12C* mutated colorectal cancer had a marked response to sotorasib with cetuximab.[73].

Finally, some of the most frequently mutated metabolic genes in human cancer are those encoding the isocitrate dehydrogenase (IDH1 and IDH2) enzymes. IDH mutations lead to a change in enzyme function, enabling efficient conversion of 2-oxoglutarate to R-2-hydroxyglutarate

(R-2-HG). Elevated cellular R-2-HG suppresses enzymes that regulate transcription and metabolism.[68] Mutations in the genes for IDH1 or IDH2 have been detected in > 20 tumor types. They are prevalent in grade II and III gliomas (>70 %) and secondary glioblastoma (55 %–88 %) (but not primary GBMs (5 %–14 %)), certain cartilaginous and bone tumors such as chondrosarcomas (20 %–80 %), acute myeloid leukemia (AML) (15 %–30 %), intrahepatic cholangiocarcinoma (6 %–30 %), angioimmunoblastic T cell lymphoma (20 %–30 %), sinonasal undifferentiated carcinoma (35 %–80 %) and solid papillary carcinoma with reverse polarity (>77 %).[69] Approved drugs include the oral IDH1 inhibitors ivosidenib and olutasidenib and the IDH2 inhibitor enasidenib.[70] Starting in 2018, ivosidenib has received a series of FDA approvals, including for *IDH1*-mutated AML, myelodysplastic syndrome, and cholangiocarcinoma. Similarly, the IDH2 inhibitor enasidenib is approved to treat *IDH2*-mutated AML. Olutasidenib is approved for patients with AML with a susceptible IDH1 mutation. Vorasidenib, a brain-penetrant inhibitor of mutant *IDH1* and *IDH2* enzymes, has shown activity in IDH-mutant gliomas.[71].

Taken together, there are multiple promising genomic biomarkers with FDA approvals across cancer types, and/or clinical trial data supporting a tissue agnostic approval. These biomarkers include aberrant *VHL, BRCA* (HRD*), ERBB2 (HER2), IDH1/2, KIT,* and *KRAS G12C,* and *NRG1*. Furthermore, specific abnormalities in the *HGF/MET*, cyclin, and *ROS1* genes, and in multiple *FGF/FGFR* family members can be found in multiple cancer types, and cognate antagonists have shown activity in case reports, case series and in clinical trials in several cancers.[74–77].

Primary and secondary resistance: Tissue is not the issue

A subject of considerable debate is whether specific molecular alterations have distinct therapeutic impact in different tissues. For instance, *BRAF V600E* mutations correlate with response to BRAF inhibitors with and without MEK inhibitors in cancers as different as hairy cell leukemia (~96 % response rate to the BRAF inhibitor vemurafenib) to melanoma (ORR ~ 50 % to vemurafenib).[78–80] Yet, disappointingly, *BRAF*-mutated colorectal cancer is less responsive. An important question emerges. Is resistance to dabrafenib plus trametinib in *BRAF V600E*-aberrant colorectal cancer because colonic tissue confers resistance or because colorectal cancer has secondary genomic pathways that are activated? The evidence points to the latter possibility. Indeed, the FDA has approved the BRAF inhibitor encorafenib together with the EGFR antibody cetuximab for *BRAF V600E*-bearing colorectal cancer because co-targeting the activated EGFR signal along with the BRAF signal is effective.[81,82] Moreover, instead of withholding a tissue-agnostic approval, the FDA elected to approve the BRAF inhibitor dabrafenib together with MEK inhibitor trametinib in solid tumors harboring *BRAF V600E* mutations, but to exclude colorectal cancer.[83].

A corollary to the question as to why some malignancies such as colorectal cancer may be unresponsive to BRAF/MEK inhibitors (i.e., due to co-activated pathways such as EGFR), is why do almost half of patients with *BRAF V600E*-mutant melanoma not respond to BRAF +/- MEK inhibitors (primary resistance) and most of the responders eventually develop progression (secondary resistance)? Is it possible that the resistance mechanisms in the non-responsive melanomas are similar, in principle, to those in the non-responsive colorectal cancers, albeit occurring less frequently – i.e., is non-responsive (primary resistance) or for that matter the emergence of secondary resistance all or mostly due to co-driver genomic alterations? And, if that is the case, is the solution, combining BRAF +/- MEK inhibitors with agents that target the co-drivers, rather than abandoning the use of the BRAF +/- MEK inhibitors in the non-responsive histologies and in the individuals with responsive histologies who show primary or secondary resistance? To date, studies that have targeted co-drivers across cancers have indeed shown that higher degrees of matching of drugs to molecular alterations via customized therapies correlate with improved outcomes.[84–86].

Biomarkers and companion diagnostics for tissue-agnostic targeting

Many gene-based drug approvals require the use of a companion diagnostic specific genomic test or, more recently, NGS, which assesses hundreds of genes. Early on, genomic companion diagnostics were often developed as single gene tests. However, as NGS gained widespread use, it quickly became apparent that testing serially for single genes was a piecemeal approach that was costly, used up tissue, and was time consuming. Instead, multiple (hundreds) of genes and their alterations could be tested simultaneously with a single NGS test. Therefore, laboratory developed clinical-grade tests and/or FDA-approved companion diagnostics that are NGS-based and interrogate either blood or tissue for hundreds of genes are most useful. These tests should provide results on genomic alterations including rearrangements/fusions, amplifications, and mutations, as well as about TMB and MSI status. NGS tests are crucial to find the biomarkers, including those that are rare or ultra-rare, for which medications exist, as well as to define specific mutations or co-drivers that mediate primary or secondary resistance,

Future biomarkers, including those that might be exploitable for tissue-agnostic approvals, may also consider tests that evaluate the downstream or composite effects of a variety of genes. For instance, *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *RAD51*, and the *FANC* genes may cause DNA repair defects leading to HRD.[44] The hallmark of HRD is the inability of a cell to successfully fix DNA double-strand breaks using the homologous recombination repair pathway. But, not all alterations in *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *RAD51*, and the *FANC* genes create the same degree of HRD. Testing for HRD is performed by probing the genome for evidence of genomic instability utilizing signatures that include: patterns of loss of heterozygosity, which are regions of intermediate size (over 15 MB and less than the whole chromosome); number of telomeric imbalances, which are the number of regions with allelic imbalance that extend to the sub-telomere but not across the centromere; and large-scale transitions, which are chromosome breaks (deletions, translocations, and inversions).[87] Hence, a test for HRD might supplement NGS as a biomarker for drugs such as PARP inhibitors or platinums.

Limitations

Despite the promise of genomics to guide treatment, there are limitations to this approach. One such issue that can arise is when there is insufficient tissue for NGS. In these instances, using blood-derived ctDNA for NGS testing may be helpful; however, ctDNA-based NGS should be considered as complementary to tissue NGS and not a substitute.[88–90] There can be discordance between what is found in tissue NGS versus blood-derived ctDNA, but these differences may reflect the different aspects of the tumor they are measuring, with blood ctDNA reflecting shed DNA from multiple tumor sites, while tissue NGS reflects the site of biopsy. Additionally, some patients may have aggressive cancers that need immediate treatment, which cannot wait for the average 2–4 weeks for NGS processing and reporting time. Reflex NGS testing at the time of biopsy might help with this situation. Another issue with the biomarker-guided approach is the cost of both NGS as well as obtaining the medications. NGS testing can cost between $1000-$4000 per assay and each of the medications can cost over $10,000 each month. Whether or not patients have access to these tests and medications is sometimes determined either by their insurance company's coverage, the drug manufacturers willingness to provide compassionate-use drug, the diagnostic company providing financial assistance, the patient's financial ability to pay, or the availability of clinical trials. Another limitation is the variety of techniques available to identify targets or matched medications; these techniques include fluorescence in situ hybridization, polymerase chain reaction, or IHCs, as well as functional assays. Each technique has differing costs and turnaround time, and specific potential targets may be more easily identifiable by one technique and not the others.[48] For instance, IHCs specifically

measures cell-derived proteins while NGS assesses the genome.

Conclusions and future directions

The observation of high response rates and benefit that is remarkably durable even in advanced cancers when drugs are matched to tumors based on biomarkers has powered a revolution in oncology clinical research and practice. This revolution has been enabled by sophisticated genomic-analyzing techniques such as NGS. NGS (the "molecular microscope") has uncovered pharmacologically tractable genomic aberrations, including those that are rare and ultra-rare, appearing in well under 1 % of cancers.

Genomic discoveries have now led to several tissue-agnostic regulatory approvals, mostly (but not exclusively) in adult solid tumors. The approvals encompass gene product-targeted drugs such as NTRK or RET or BRAF inhibitors and immune-targeted drugs such as anti-PD1 agents in the solid tumor field, as well as an FGFR1 inhibitor in hematologic malignancies (Fig. 1). Furthermore, there are now a wealth of emerging tissue-agnostic targets: *ALK, BRCA, ERBB2 (*HER2*), IDH1/2, KIT, KRAS G12C, NRG1* and *VHL,* as well as functional biomarkers such as HRD. Indeed, tissue-agnostic therapy may be a paradigm, rather than an exception, since it is the molecular defect that drives cancer. Despite this approach having validity in a great deal of settings, not all patients and settings derive salutary effects from genomically selected therapies. As with traditional organ-of-origin treatments and approvals, there can be considerable heterogeneity in terms of response rates; for example, targeting *BRAF V600E* may be effective in both solid tumors and hematologic malignancies, but the response rates range from 12 % (colorectal cancer) to near 100 % (hairy cell leukemia). Consequently, the medication pair – dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) – is FDA-approved for *BRAF V600E*-altered solid cancers that are not colorectal cancer. Importantly, in colorectal cancer, when an additional agent is added — the EGFR antibody cetuximab — the initial resistance to BRAF inhibition can be overcome and yield benefit for patients with *BRAF V600E*-altered colorectal cancer—with the BRAF inhibitor encorafenib together with cetuximab approved for *BRAF V600E* colorectal cancer. The latter data suggest that resistance to targeted agents may be due to secondary oncogenic drivers/signals that can be elucidated by molecular studies and must be co-targeted. Notably, resistance mediated by molecular co-drivers may exist on a continuum and, in addition to accounting for primary resistance in less responsive histologies such as *BRAF*-mutated colorectal cancer (when treated with BRAF/MEK inhibitors), may also explain primary and secondary resistance in BRAF inhibitor-responsive tissues such as melanoma as well. Moreover, primary, and secondary drug resistance due to co-drivers may be operative across cancers and account for treatment failure. If that is the case, the issue that may need to be addressed is understanding the molecular drivers in individual cancers, rather than just the tissue origins of the cancer.

One of the important benefits of tissue-agnostic approvals is that they provide the opportunity for drug access across multiple tissue types, including for patients afflicted with rare and ultra-rare cancers. Such conditions embody a huge unmet need in that it is improbable that they will have their own trials, especially in the setting of an infrequent/ultra-rare molecular alteration.

In summary, a wealth of data demonstrate that cancer is a disease of the genome and that biomarker-based tissue-agnostic strategies can yield responses rates that are high and benefit that is remarkably durable for both matched gene- and immune-targeted agents. Future consideration should be given to expanding tissue-agnostic basket clinical trials so that they become master platform studies that encompass both hematologic and solid malignancies, germline and somatic alterations, and both children and adults. Furthermore, in order to fully interrogate tumors, multi-omic technology beyond that which is DNA based should be exploited in order to gain a better understanding of molecular drivers /co-drivers that mediate sensitivity and resistance across malignancies and the need for customized combinations. Finally, a large body of evidence now suggests that validated molecular biomarkers are pharmacologically tractable across cancers – it it's a target, it's a pan-cancer target.

CRediT authorship contribution statement

JJA: Writing - original draft, Writing - review & editing. **SK:** Writing - review & editing. **JKS:** Writing - review & editing. **SML:** Writing - review & editing. **RK:** Conceptualization, Writing - original draft, Writing - review & editing, Visualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [**JJA** serves on the advisory board of CureMatch Inc and as a consultant for datma. **SK** serves as a consultant for Foundation Medicine. He receives speaker's fee from Roche and advisory board for Pfizer. He has research funding from ACT Genomics, Sysmex, Konica Minolta and OmniSeq. **JKS** receives research funding from Amgen Pharmaceuticals and Foundation Medicine, consultant fees from Deciphera, speaker's fees from Deciphera, Foundation Medicine, La-Hoffman Roche, Merck, MJH Life Sciences, and QED Therapeutics **SLM** is the co-founder of io9 and is on Biological Dynamics, Inc. Scientific Advisory Board. **RK** has received research funding from Boehringer Ingelheim, Debiopharm, Foundation Medicine, Genentech, Grifols, Guardant, Incyte, Konica Minolta, Medimmune, Merck Serono, Omniseq, Pfizer, Sequenom, Takeda, and TopAlliance and from the NCI; as well as consultant and/or speaker fees and/or advisory board/consultant for Actuate Therapeutics, AstraZeneca, Bicara Therapeutics, Inc., Biological Dynamics, Caris, Datar Cancer Genetics, Daiichi, EISAI, EOM Pharmaceuticals, Iylon, LabCorp, Merck, NeoGenomics, Neomed, Pfizer, Precirix, Prosperdtx, Regeneron, Roche, TD2/Volastra, Turning Point Therapeutics, X-Biotech; has an equity interest in CureMatch Inc. and IDbyDNA; serves on the Board of CureMatch and CureMetrix, and is a co-founder of CureMatch.].

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