Tumor-Agnostic Precision Medicine from the AACR GENIE Database: Clinical Implications

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ABSTRACT

Biomarker-driven cancer therapy has revolutionized precision oncology. With a better understanding of tumor biology, tissue-agnostic targets have been characterized and explored, which ultimately led to therapeutics with pan-cancer efficacy. To date, five molecular biomarkers have obtained FDA tissue-agnostic approval for targeted therapies and immunotherapies. Those include $BRAF^{V600E}$ mutations, RET fusions, $NTRK$ fusions, high tumor mutation burden (TMB), and deficient mismatch repair/high microsatellite instability (dMMR/MSI-High). Herein, we have used data from AACR project GENIE to explore the clinico-genomic landscape of these alterations. AACR GENIE is a publicly accessible registry of genomic data from multiple collaborating cancer centers. Current database (version 13.0) includes sequencing data of 168,423 samples collected from patients with different cancers. We were able to identify $BRAF^{V600E}$, RET fusions, $NTRK$ fusions, and high TMB in 2.9%, 1.6%, 1.5%, and 15.2% of pan-cancer samples, respectively. In this article, we describe the distribution of those tissue-agnostic targets among different cancer types. In addition, we summarize the current prospect on the biology of these alterations and evidence on approved drugs, including pembrolizumab, dostarlimab, larotrectinib, entrectinib, selpercatinib, and dabrafenib/trametinib combination.

Introduction

For decades, cancer management has relied primarily on microscopic examination of tumor tissue with focus on understanding its exact pathology, including the extent of infiltration and the tissue of origin (1). Tumors have been, therefore, managed according to their location in the human body and management guidelines have made this distinction clear by being developed in a site-specific approach. Moreover, cancer research, cancer clinical trials, and anticancer drugs were all developed on the basis of histology and site. However, with the rapid evolution that happened in clinical genomic testing and contemporaneous advances in the development of precision cancer therapies, genomically targeted therapies and agents that arm the immune system have been introduced.

The list of targeted therapies, that act on specific molecular alterations, has exponentially grown in the past decade (2). Moreover, the introduction of immunotherapy has brought cancer therapeutics to the next level by enabling the patients' body itself to fight cancer (3). That being said, beyond the era of site-specific cancer management, tissue-agnostic biomarkers across different cancer histologies have emerged. This was mainly driven by actionable alterations identified by next-generation sequencing (NGS) and the availability of medicines

that can target these alterations. Although this appeared hypothetical, the past few years have brought some evidence on the efficacy of such biomarker-driven tissue-agnostic therapeutics; and regulatory approvals have driven the paradigm shift for these tissue-agnostic therapies. So far, six therapies have been approved by the FDA for tissue-agnostic indications based on molecular alterations (2, 4). More such tissue-agnostic therapies albeit in rare subsets of cancers are on the horizon with similar potential and the list is only expected to grow more in the future.

Herein, we review the current landscape of tissue-agnostic targets, distribution among different tumor types, and therapeutics that are being used to target. Moreover, we review data from 148,268 patients (168,423 samples) from the AACR project GENIE (version 13; ref. 5) to elaborate on the length and breadth of the clinical and molecular landscapes of those alterations.

Molecular Biomarkers and Targets in Tissue-Agnostic Approvals

To date, five biomarkers have received regulatory approval for tissue-agnostic therapies (**Table 1**: (i) mismatch repair deficient (dMMR) or high microsatellite instability (MSI) cancers, (ii) tumor mutational burden-high (TMB-H) cancers (≥10 mutations per megabase; mut/Mb), (iii) $NTRK$ fusion-positive cancers, (iv) RET fusion-positive cancers, and (v) $BRAF^{V600E}$-mutant cancers other than colorectal cancers. In the AACR project GENIE, 4,912 samples harbored $BRAF^{V600E}$ mutations (2.9%), 410 harbored $NTRK$ fusions (0.24% of all samples and 1.6% of samples profiled for structural variants), and 396 harbored RET fusions (0.26% of all samples and 1.5% of samples profiled for structural variants). In addition, 25,527 samples (15.2%) were classified as having high TMB. There are no data on dMMR or MSI in AACR GENIE although other studies have suggested a pan-cancer prevalence of around 3% (refs. 6, 7; **Fig. 1**).

$BRAF^{V600E}$ Mutations

$BRAF^{V600E}$ is a mutation that commonly occurs in the MAPK pathway leading to unregulated cell growth and differentiation (8, 9). The V600E alteration is part of the $BRAF$ class I mutations that are

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Table 1. Biomarkers currently with drugs that have FDA approval for a tissue agnostic indication.

Biomarker/target	Approved drug(s)	Year of FDA approval
dMMR	Pembrolizumab	2017
	Dostarlimab	2022
MSI-H	Pembrolizumab	2017
TMB-High	Pembrolizumab	2020
$BRAF^{V600E}$	Dabrafenib + Trametinib	2022
RET fusions	Selpercatinib	2022
$NTRK$ fusions	Larotrectinib	2018
	Entrectinib	2019

RAS-independent. Therefore, such mutation would lead to maintained active cell signaling via the MAPK pathway without upstream activation via RAS (10–12).

In AACR Project GENIE (version 13), we identified $BRAF^{V600E}$ mutations in 4,912 out of 167,387 profiled samples for $BRAF$ mutations accounting for nearly 3% of the pan-cancer cohort. The most common cancers with $BRAF^{V600E}$ mutations were melanoma ($n = 1,379$; 28.1%), colorectal cancer ($n = 1,228$; 25%), thyroid cancer ($n = 922$; 18.8%), glioma ($n = 392$; 8%), non–small cell lung cancer (NSCLC; $n = 329$; 6.7%); among multiple other tumor types (13.5%). The most frequent cooccurring alterations were $TERT$ and $TP53$ (Supplementary Table S1). Cancers with the highest frequency of $BRAF^{V600E}$ alterations were thyroid cancer ($n = 922$; 40.2%), melanoma ($n = 1,379$; 20.3%), histiocytosis ($n = 91$; 17.3%), colorectal cancer ($n = 1,228$; 7.9%), miscellaneous brain tumor ($n = 16$; 5.2%), glioma ($n = 392$; 3.9%), non-melanoma skin cancer ($n = 46$; 3.8%), gastrointestinal neuroendocrine tumors ($n = 25$; 3.7%), small bowel cancer ($n = 12$; 2.6%), and Wilms tumor ($n = 4$; 2.1%; **Table 2**). Cancers with a high frequency of $BRAF^{V600E}$ (≥1%) but a low number of profiled samples (<100) included primary central nervous system (CNS) melanocytic tumors ($n = 3/7$; 42.9%); melanocytoma ($n = 4/13$; 30.8%); head and neck cancer, not otherwise specified (NOS; $n = 1/8$; 12.5%); gastrointestinal neuroendocrine tumors of the esophagus/stomach ($n = 1/11$; 9.1%); angiomatoid fibrous histiocytoma ($n = 1/14$; 7.1%); parathyroid cancer ($n = 2/29$; 6.9%); tubular adenoma of the colon ($n = 2/44$; 4.5%); non-Hodgkin lymphoma ($n = 1/62$; 1.6%); and peritoneal cancer, NOS ($n = 1/86$; 1.2%).
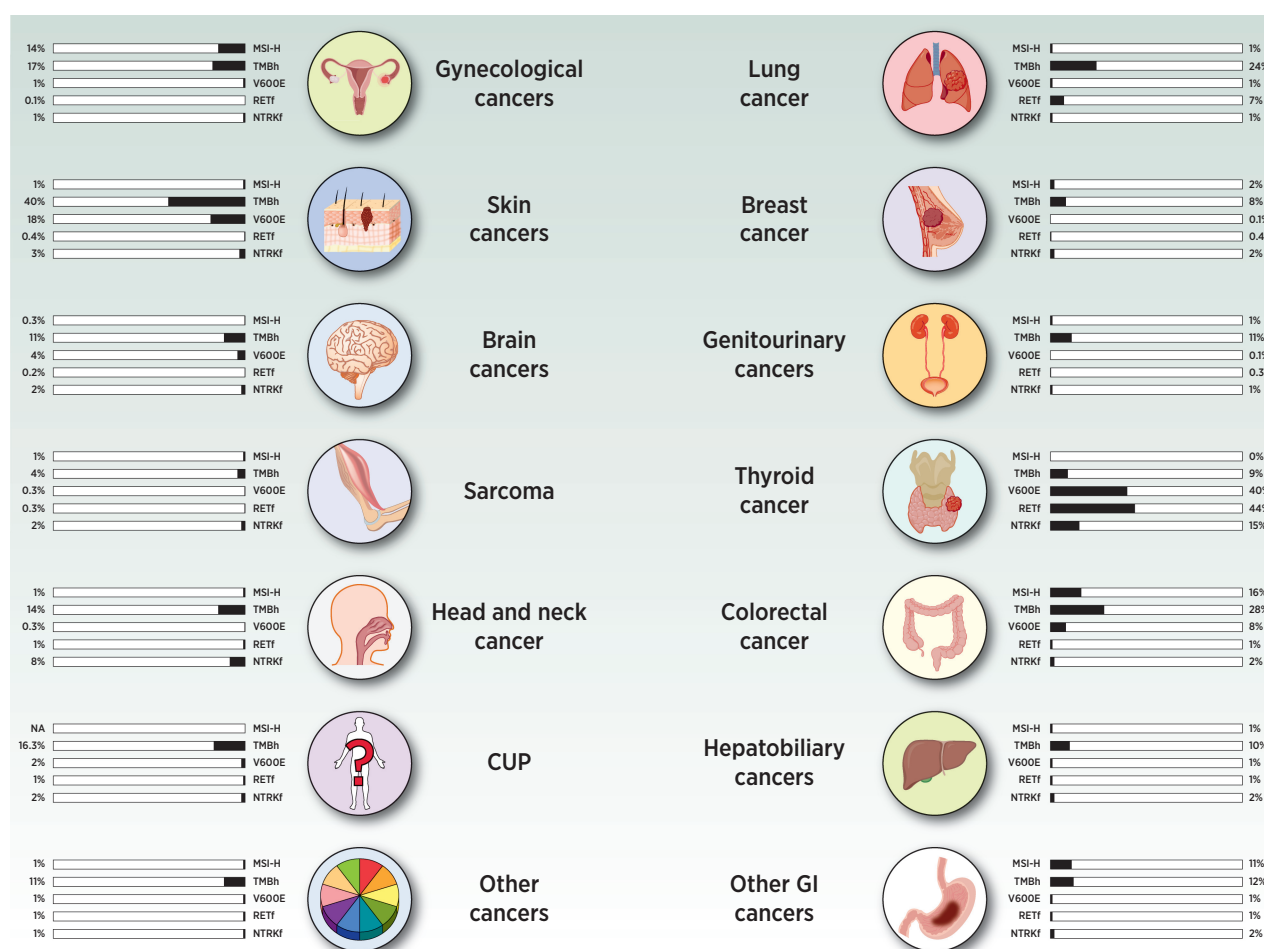

Figure 1.
Frequency of tissue-agnostic targets across common malignancies. Data on $BRAF$ V600E, RET fusions, $NTRK$ fusions, and TMB are obtained from AACR GENIE database. Data on dMMR/MSI-H are obtained through literature search as they are not available in GENIE.

Table 2. Frequency of tissue-agnostic targets in different cancer types (alphabetically arranged) in AACR GENIE v13.

Cancer type	Alteration frequency				
	$BRAF^{V600E}$	*RET* fusion	*NTRK* fusion	TMB-high (> 16)	TMB-high (≥ 10)
Ampullary cancer	1.1% ($n = 4$)	0% ($n = 0$)	5.1% ($n = 2$)	13% ($n = 46$)	19.3% ($n = 68$)
Anal cancer	0% ($n = 0$)	2% ($n = 1$)	2% ($n = 1$)	12% ($n = 44$)	19.9% ($n = 73$)
Appendiceal cancer	1.2% ($n = 9$)	0% ($n = 0$)	2.1% ($n = 1$)	14.6% ($n = 108$)	18.5% ($n = 137$)
Bladder cancer	0.1% ($n = 6$)	0.3% ($n = 3$)	1% ($n = 9$)	20.3% ($n = 947$)	38.8% ($n = 1,813$)
Breast cancer	0.1% ($n = 17$)	0.4% ($n = 13$)	1.4% ($n = 41$)	7.7% ($n = 1,235$)	11.7% ($n = 1,874$)
Cancer of unknown primary	1.6% ($n = 86$)	1% ($n = 8$)	1.5% ($n = 12$)	15.2% ($n = 815$)	23.4% ($n = 1,249$)
Cervical cancer	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	11.5% ($n = 100$)	18.2% ($n = 158$)
Colorectal cancer	7.9% ($n = 1,228$)	0.9% ($n = 15$)	1.7% ($n = 29$)	26.8% ($n = 4,145$)	31.9% ($n = 4,937$)
Endometrial cancer	0.1% ($n = 4$)	0.1% ($n = 1$)	0.5% ($n = 4$)	24.7% ($n = 1,257$)	30.4% ($n = 1,549$)
Esophagogastric cancer	0.1% ($n = 6$)	0.7% ($n = 8$)	1.8% ($n = 20$)	11.4% ($n = 541$)	17.2% ($n = 817$)
Gastrointestinal neuroendocrine tumor	3.7% ($n = 25$)	0% ($n = 0$)	5.4% ($n = 3$)	4% ($n = 27$)	6.6% ($n = 45$)
Gastrointestinal stromal tumor	0.4% ($n = 6$)	0% ($n = 0$)	0.8% ($n = 1$)	14.4% ($n = 222$)	14.6% ($n = 226$)
Germ cell tumor	0.1% ($n = 1$)	0% ($n = 0$)	1.1% ($n = 1$)	2.2% ($n = 23$)	2.9% ($n = 31$)
Glioma	3.9% ($n = 392$)	0.3% ($n = 6$)	1.8% ($n = 43$)	9.8% ($n = 988$)	11.1% ($n = 1,121$)
Head and neck cancer	0.05% ($n = 1$)	0.8% ($n = 2$)	0.8% ($n = 2$)	15.6% ($n = 344$)	24.9% ($n = 548$)
Hepatobiliary cancer	1.1% ($n = 39$)	0.5% ($n = 3$)	1.6% ($n = 10$)	8.4% ($n = 291$)	12% ($n = 413$)
Histiocytosis	17.3% ($n = 91$)	8% ($n = 2$)	0% ($n = 0$)	2.7% ($n = 14$)	2.7% ($n = 14$)
Hodgkin lymphoma	0% ($n = 0$)[a]	0% ($n = 0$)	0% ($n = 0$)	4.8% ($n = 6$)	7.9% ($n = 10$)
Leukemia	0.2% ($n = 9$)	0% ($n = 0$)	0% ($n = 0$)	22.8% ($n = 1,351$)	28% ($n = 1,660$)
Melanoma	20.3% ($n = 1,379$)	0.1% ($n = 1$)	2.6% ($n = 18$)	39.8% ($n = 2,709$)	49.1% ($n = 3,338$)
Mesothelioma	0.1% ($n = 1$)	0% ($n = 0$)	1% ($n = 2$)	2% ($n = 19$)	2.8% ($n = 27$)
Non-Hodgkin lymphoma	1.6% ($n = 1$)	0% ($n = 0$)	0% ($n = 0$)	8.1% ($n = 5$)	9.7% ($n = 6$)
NSCLC	1.4% ($n = 329$)	5.7% ($n = 215$)	0.9% ($n = 33$)	22.6% ($n = 5,447$)	33.8% ($n = 8,142$)
Ovarian cancer	0.9% ($n = 56$)	0% ($n = 0$)	0.6% ($n = 7$)	10.3% ($n = 630$)	12.8% ($n = 783$)
Pancreatic cancer	0.4% ($n = 26$)	0.1% ($n = 1$)	1.8% ($n = 15$)	10.3% ($n = 706$)	11.9% ($n = 820$)
Parathyroid cancer	6.9% ($n = 2$)	0% ($n = 0$)[a]	0% ($n = 0$)[a]	44.8% ($n = 13$)	44.8% ($n = 13$)
Penile cancer	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	17.5% ($n = 11$)	25.4% ($n = 16$)
Prostate cancer	0.02% ($n = 1$)	0.2% ($n = 4$)	0.4% ($n = 8$)	4.2% ($n = 239$)	5.4% ($n = 312$)
Renal cell carcinoma	0% ($n = 0$)	0.5% ($n = 1$)	0% ($n = 0$)	4.4% ($n = 115$)	6.2% ($n = 160$)
Salivary gland cancer	0.7% ($n = 7$)	0.5% ($n = 1$)	15.3% ($n = 29$)	6.3% ($n = 64$)	9.2% ($n = 93$)
Sex cord stromal tumor	0% ($n = 0$)[a]	0% ($n = 0$)	0% ($n = 0$)	3.8% ($n = 9$)	4.6% ($n = 11$)
Skin cancer, nonmelanoma	3.8% ($n = 46$)	1.6% ($n = 3$)	6.4% ($n = 12$)	32.6% ($n = 396$)	36.9% ($n = 448$)
Small bowel cancer	2.6% ($n = 12$)	0% ($n = 0$)	0% ($n = 0$)	26.7% ($n = 124$)	35.3% ($n = 164$)
Small cell lung cancer	0% ($n = 0$)	0.7% ($n = 1$)	0.7% ($n = 1$)	16.3% ($n = 151$)	35.8% ($n = 332$)
Soft tissue sarcoma	0.3% ($n = 16$)	0.3% ($n = 4$)	2.3% ($n = 34$)	4.1% ($n = 202$)	5.8% ($n = 287$)
Thyroid cancer	40.2% ($n = 922$)	36% ($n = 96$)	17.2% ($n = 46$)	8.7% ($n = 199$)	10.1% ($n = 231$)
Uterine sarcoma	0.1% ($n = 1$)	0.6% ($n = 1$)	2.3% ($n = 4$)	5.1% ($n = 36$)	6% ($n = 42$)
Vaginal cancer	0% ($n = 0$)	0% ($n = 0$)	0% ($n = 0$)	11.4% ($n = 19$)	21.6% ($n = 36$)
Vulvar carcinoma	0% ($n = 0$)[a]	0% ($n = 0$)[a]	0% ($n = 0$)[a]	0% ($n = 0$)	33.3% ($n = 1$)
Wilms tumor	2.1% ($n = 4$)	0% ($n = 0$)	0% ($n = 0$)	4.7% ($n = 9$)	4.7% ($n = 9$)

Note: Additional cancer types are presented in Supplementary Table S2.
[a]It is possible that gene might have not been profiled for this alteration.

$BRAF^{V600E}$ can be targeted by using inhibitors of BRAF and MEK (12). On the basis of multiple studies showing dramatic efficacy in $BRAF^{V600E}$-positive melanoma, three different BRAF/MEK inhibitor combinations have received FDA approval, including dabrafenib and trametinib. Further studies in NSCLC and anaplastic thyroid cancer led to the approval of dabrafenib + trametinib combination in these tumor types (2, 13–49). Dabrafenib plus trametinib is a BRAF inhibitor that when combined with the MEK inhibitor trametinib leads to synergistic blockade of the BRAF/MEK pathway and control of cellular-signaling that triggers aberrant cell proliferation (50–52). The exception for this activity is colorectal cancer due to an EGFR-dependent feedback mechanism that causes a paradoxical response to BRAF inhibitors and can be controlled by using EGFR inhibitors like cetuximab (53–55). Recently, dabrafenib and trametinib received United States FDA approval for $BRAF^{V600E}$-positive solid tumors. This was based on pooled data from the ROAR study (BRF117019; NCT02034110),

NCI-MATCH (NCT02465060), and CTMT212×2101 (NCT02124772; refs. 35–40), and was supported with prior analysis in melanoma and NSCLC studied as part of COMBI-d (NCT01584648), COMBI-v (NCT01597908), and BRF113928 (NCT01336634) trials (26–28, 31–34). In 131 adult and 36 pediatric patients, the objective response rate (ORR) was 41% and 25% in adult and pediatric patients; respectively (ref. 55; **Fig. 2**).

RET Fusions

Chromosomal rearrangements can lead to functional changes, which occur as part of oncogenesis (56–70). Fusions that occur in the *RET* gene, coding for a transmembrane tyrosine kinase with downstream activating action on multiple cellular pathways, were first reported in 1990 (56–70) in papillary thyroid carcinoma and demonstrated to associate with unregulated cellular-signaling via ligand-independent activation (56–70).
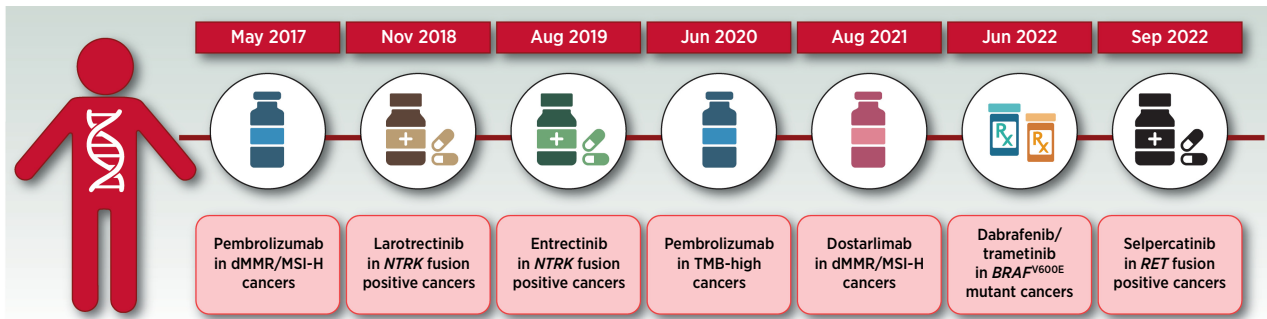
Figure 2.
Timeline of FDA tissue-agnostic approvals. (Adapted from an image created with BioRender.com.)

Later, other *RET* fusions were detected, characterized, and shown to drive cancer development in multiple other tumor types (56–70).

In AACR Project GENIE (version 13), 396 *RET* fusion-positive samples were identified among 25,792 profiled samples for *RET* structural variants (1.5%). *RET* fusions were identified in patients with NSCLC (*n* = 215; 54.3%), thyroid cancer (*n* = 96; 24.2%), colorectal cancer (*n* = 15; 3.8%), breast cancer (*n* = 13; 3.3%), cancer of unknown primary (*n* = 8; 2%), esophagogastric cancer (*n* = 8; 2%), and multiple other tumor types (10.4%). Fusion partners that were most frequently observed were *KIF5B, CCDC6,* and *NCOA4.* The most frequent cooccurring alterations included *TP53* and *SETD2* mutations (Supplementary Table S1). In disease-specific analysis, cancers with the highest prevalence of *RET* fusions were thyroid cancer (*n* = 96; 36%), NSCLC (*n* = 215; 5.7%), anal cancer (*n* = 1; 2%), miscellaneous brain tumors (*n* = 1; 1.7%), non-melanoma skin cancer (*n* = 3; 1.6%), nerve sheath tumor (*n* = 1; 1.1%), cancer of unknown primary (*n* = 8; 1%), mature T and natural killer (NK) neoplasms (*n* = 1; 1%), colorectal cancer (*n* = 15; 0.9%), and head and neck cancer (*n* = 2; 0.8%; **Table 2**). Other tumors with a high frequency of *RET* fusions (≥1%) but a low number of profiled samples (<50) included pheochromocytoma (*n* = 1/2; 50%), histiocytosis (*n* = 2/25; 8%), and peripheral nervous system tumors (*n* = 1/49; 2%).

The ATP-dependent selective *RET* inhibitor, selpercatinib, is approved by FDA for solid tumors with *RET* fusions (71). Selpercatinib leads to the cessation of upstream *RET*-dependent activation which when aberrant leads to unbridled activation of multiple cellular-signaling pathways, including PI3K, RAS, and JAK (65–69, 72, 73). The FDA approval was based on data from the LIBRETTO-001 (NCT03157128) basket trial that evaluated the use of selpercatinib in multiple solid tumors. Responses were initially observed in NSCLC and thyroid cancer (ORR of 85% and 64%, 73% and 69%, for untreated and pretreated NSCLC and patients with thyroid cancer; respectively; refs. 74, 75). Further analysis in other tumor types revealed similar activity in different non-thyroid and non-lung cancers with an ORR of 43.9% which was the basis for FDA approval (ref. 4; **Fig. 2**).

NTRK Fusions

The first discovery of fusions involving *NTRK* genes was in 1998 in congenital fibrosarcoma (76). Multiple other tumors were shown to be driven by other fusions involving the *NTRK* family of genes; *NTRK1, NTRK2,* and *NTRK3.* Such structural abnormalities can lead to activation of downstream pathways independent on ligand-binding, and therefore can lead to uncontrolled cancerous proliferation (77).

In AACR Project GENIE (version 13), we were able to identify *NTRK* fusions (affecting either *NTRK1, NTRK2, or NTRK3* genes) in 410 out of 25,792 profiled samples for *NTRK* structural variants (1.6%). *NTRK* fusions were primarily observed in thyroid cancer (*n* = 46; 11.2%), glioma (*n* = 43; 10.5%), breast cancer (*n* = 41; 10%), soft tissue sarcomas (*n* = 34; 8.3%), and NSCLC (*n* = 33; 8%), among other tumor types (52%). The most common fusion partners were *ETV6*, intragenic fusions, and *TPM3*. Again, the most frequent cooccurring mutations were detected in *TP53* and *TERT* (Supplementary Table S1). The highest frequency of *NTRK* fusions was observed in thyroid cancer (*n* = 46; 17.2%), salivary gland cancer (*n* = 29; 15.3%), miscellaneous brain tumor (*n* = 6; 10.3%), nonmelanoma skin cancer (*n* = 12; 6.4%), gastrointestinal neuroendocrine tumor (*n* = 3; 5.4%), melanoma (*n* = 18; 2.6%), soft tissue sarcoma (*n* = 34; 2.3%), uterine sarcoma (*n* = 4; 2.3%), anal cancer (*n* = 1; 2%; **Table 2**), and B-lymphoblastic leukemia/lymphoma (*n* = 2; 2%). Other cancers with high frequency of NTRK fusions (≥1%) but low number of profiled samples (<50) included infantile fibrosarcoma (*n* = 3/3; 100%), ampullary cancer (*n* = 2/39; 5.1%), peripheral nervous system tumors (*n* = 2/49; 4.1%), miscellaneous neuroepithelial tumors (*n* = 1/41; 2.4%), and appendiceal cancer (*n* = 1/48; 2.1%)

NTRK fusions can be targeted using larotrectinib and entrectinib (78, 79). Both agents have received FDA approval for a tissue-agnostic indication in patients with solid tumors who harbor *NTRK* fusions (78, 79). The efficacy of larotrectinib in patients with *NTRK* gene fusions was evaluated in the context of three clinical trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). In a pooled analysis of 55 patients, the ORR was 75%, and the median duration of response was 32.9 months (80). Entrectinib was approved on the basis of a pooled analysis of ALKA-372–001 (NCT02097810), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267) trials. The ORR was 59% in 54 evaluable patients with *NTRK* gene fusions (ref. 81; **Fig. 2**).

TMB-High

TMB reflects the number of genetic alterations in the genome of cancer cells. Its importance in cancer management comes from the hypothetical notion of higher odds of immune system recognition of cancerous cells that have a higher number of mutations (82). Practically, TMB can be calculated using data from NGS of either tissue or plasma and is reported as the number of mutations per megabase (mut/MB). Cutoffs used for defining TMB high and low

cancers have been variable, but at least there is a consensus that cancers with 10 or more mutations per megabase would behave differently in terms of triggering immune response (82–84).

In AACR Project GENIE (version 13), nearly 15.2% ($n = 25{,}527$) of pan-cancer samples ($n = 167{,}423$) were classified as TMB-high tumors using the classification algorithm developed by GENIE. Data on calculated TMB were provided to investigators by AACR GENIE team upon request. Those included TMB calculated raw data as well as groups based on a classifier that was used in GENIE (low: <2, intermediate: 2–16, and high: >16 TMB subgroups). The most frequent diagnoses in TMB-high tumors were NSCLC ($n = 5{,}447$; 21.3%), colorectal cancer ($n = 4{,}145$; 16.2%), melanoma ($n = 2{,}709$; 10.6%), leukemia ($n = 1{,}351$; 5.3%), and endometrial cancer ($n = 1{,}257$; 4.9%), among others (41.6%). Tumors with highest frequency of TMB-high samples included melanoma ($n = 2{,}709$; 39.8%), non-melanoma skin cancer ($n = 396$; 32.6%), myelodysplastic/myeloproliferative neoplasms ($n = 174$; 28.9%), colorectal cancer ($n = 4{,}145$; 26.8%), small bowel cancer ($n = 124$; 26.7%), endometrial cancer ($n = 1{,}257$; 24.7%), leukemia ($n = 1{,}351$; 22.8%), NSCLC ($n = 5{,}447$; 22.6%), bladder cancer ($n = 947$; 20.3%), and myeloproliferative syndromes ($n = 419$; 19.5%). Cancers with a high frequency of TMB high ($\geq 15\%$) but a low number of profiled samples (<100) included bowel cancer, NOS ($n = 2/3$; 66.7%), lung cancer, NOS ($n = 15/27$; 55.6%), parathyroid cancer ($n = 13/29$; 44.8%), thyroid cancer, NOS ($n = 3/9$; 33.3%), vulvar/vaginal cancer, NOS ($n = 1/3$; 33.3%), uterine cancer, NOS ($n = 1/3$; 33.3%), adenocarcinoma *in situ* ($n = 1/4$; 25%), penile cancer ($n = 11/63$; 17.5%), and bladder/urinary tract cancer, NOS ($n = 1/6$; 16.7%; **Table 2**). *RET* fusions, *NTRK* fusions, and *BRAF*[V600E] mutations were simultaneously identified in 15 (0.06%), 37 (0.1%), and 1440 (5.6%) samples with high TMB.

Because TMB data from AACR GENIE bins only tumors with TMB > 16 as high TMB cancers, we have also performed an exploratory analysis to reclassify tumors using 10 mut/mb as cutoff, which is considered the cutoff used for defining the tissue-agnostic indication of pembrolizumab by FDA. Using that classification, 34,874 samples (20.3% of pan-cancer samples) had ≥ 10 mut/mb and were classified as having high TMB. Cancers with highest frequency of TMB high samples using that classification included melanoma ($n = 3{,}338$; 49.1%), bladder cancer ($n = 1{,}813$; 38.8%), non-melanoma skin cancer ($n = 448$; 36.9%), small cell lung cancer ($n = 332$; 35.8%), small bowel cancer ($n = 164$; 35.3%), NSCLC ($n = 8{,}142$; 33.8%), myelodysplastic/myeloproliferative neoplasms ($n = 203$; 33.7%), colorectal cancer ($n = 4{,}937$; 31.9%), endometrial cancer ($n = 1{,}549$; 30.4%), and leukemia ($n = 1{,}660$; 28%; **Table 2**).

The FDA approval of pembrolizumab, an antibody blocker of PD-1, for solid tumors with high TMB was based on retrospective analysis of 102 patients with high TMB (≥ 10 mut/mb) advanced solid tumors in the KEYNOTE-158 trial (NCT02628067). The ORR was 29% with a median duration of response that was not reached at the time of data cutoff. In a subgroup analysis of patients with ≥ 13 mut/Mb ($n = 70$), the ORR increased to 37% with a median duration of response that is not reached (ref. 85; **Fig. 2**).

dMMR/MSI-H

Mismatch repair genes are responsible for fixing DNA damage that results during DNA replication. Therefore, deficiency leads to loss of genomic integrity and accumulation of mutations, including regions of repetitive DNA sequences also known as microsatellites. Cancers with dMMR/MSI-H generally confer a poor prognosis due to the hypermutable status (7).

The AACR project GENIE does not currently contain data on dMMR/MSI-H tumors. We have performed a review of literature to expand on landscape of MSI-H in different tumor types, which varied substantially between different studies. Bonneville and colleagues (7) analyzed whole exome data from 11,139 tumor-normal paired samples from 11,080 patients with 39 cancer types. They were able to detect MSI in 27 of 39 types of cancer with a variable disease-specific distribution. The highest frequency was observed in endometrial carcinoma ($n = 170$; 31.37%), colon adenocarcinoma ($n = 85$; 19.72%), stomach adenocarcinoma ($n = 84$; 19.09%), rectal adenocarcinoma ($n = 9$; 5.73%), adrenocortical carcinoma ($n = 4$; 4.35%), uterine carcinosarcoma ($n = 2$; 3.51%), cervical cancer ($n = 8$; 2.62%), Wilms tumor ($n = 1$; 2.44%), mesothelioma ($n = 2$; 2.41%), and esophageal carcinoma ($n = 3$; 1.63%; ref. 7). Another meta-analysis of published studies included data from 28,213 patients, where MSI-H was estimated to be prevalent in nearly 2.7%–2.9% of samples in the pooled analysis. Highest prevalence was reported in endometrial cancer (21.9%), small bowel cancer (14.3%), colon cancer (13%), colorectal cancer (10.2%), and gastric cancer (8.5%; ref. 6).

Immunotherapies are potential options for patients with dMMR/MSI-H tumors. Currently, the FDA approved the PD-1 blockers pembrolizumab and dostarlimab for dMMR/MSI-H tumors regardless of tissue of origin (86, 87). Data leading to FDA tissue-agnostic indication of pembrolizumab in 2017 came from five clinical trials: KEYNOTE-016 (NCT01876511), KEYNOTE-164 (NCT02460198), KEYNOTE-012 (NCT01848834), KEYNOTE-028 (NCT02054806), and KEYNOTE-158 (NCT02628067), which assessed the use of pembrolizumab in dMMR or MSI-H tumors. In a pooled analysis of 149 patients, the ORR was 39.6%, and the median duration of response was not reached at data cutoff (88). In 2021, dostarlimab was also approved for solid tumors with dMMR on the basis of data from the GARNET trial (NCT02715284) that evaluated the drug in 209 patients and showed an ORR of 41.6% and a median duration of response of 34.7 months (ref. 89; **Fig. 2**). More recently, there became interest in the use of PD-1 blockade in the neoadjuvant setting. In a phase II study where dostarlimab was used in patients with dMMR/MSI-H locally advanced rectal cancer, all patients treated ($n = 12$) had clinical complete response and no evidence of disease on PET/CT, MRI, digital rectal examination, or biopsy (90). While the study was including only patients with a rectal cancer, such outstanding result aligning with prior data that led to tissue-agnostic approvals can open the door for lots of future possibilities; including the possibility of moving tissue-agnostic treatments to neoadjuvant setting.

Special Situations: Carcinoma of Unknown Primary

One interesting finding we observed was the presence of tissue-agnostic biomarkers in a substantial portion of patients with carcinoma of unknown primary (1.6%, 1%, 1.5%, 15.2% for *BRAF*[V600E] mutations, *RET* fusions, *NTRK* fusions, and TMB high samples, respectively). With targetable alterations in those patients, the chances of improved outcomes or even cure are rising in a category of patients that long suffered from a historically poor prognosis due to the inability to determine the tissue of origin (91). In an era of changing landscape of tumor identity from microscopic tissue–based diagnosis to genomic alteration–based diagnosis, carcinoma of unknown primary emerges as the perfect prototype to prove the hypothesis given its historical resistance to conventional treatment options. In fact, newer technologies, including liquid biopsy, have made genetic testing a practical and feasible option in those patients that can drive the paradigm change led by molecularly-targeted therapeutics (92).

Special Situations: Rare Tumors

The beauty of tissue-agnostic precision oncology is its ability to treat cancers with low incidence rates that have been less frequently studied or profiled (93–95). Interestingly, our analysis of AACR GENIE revealed the presence of tissue-agnostic targets in a wide variety of cancers with low incidence and prevalence (**Table 2**; Supplementary Table S2). This was evident through the analysis that we performed for tumors with a low number of profiled samples that showed the strong presence of those biomarkers as aforementioned. Although data will remain statistically inconclusive given the limitation of a small sample size that is inappropriate for generalization, this can at least provide a proof of concept on the importance of molecular profiling in those patients and that it can lead to expanded treatment options beyond current standards of care.

Ongoing Promising Targets and Biomarkers

There are many emerging targets that have the potential in the future as tissue-agnostic biomarkers given promising data from early clinical studies in different tumor types and ongoing basket trials. For example, there is compelling clinical evidence supporting the use of zenocutu-zumab in patients with *NRG1* fusion–positive solid tumors, repotrecti-nib in patients with *NTRK1/2/3* fusion–positive solid tumors, and PC14586 in patients with *TP53* Y220C mutations (2). Other targets of potential interest that are being tested in clinical trials with promising results include HER2/neu and *FGFR2* fusions (4, 96). Moreover, there is at least biological evidence to support hypothesis in favor of multiple other targets which are currently being explored in early clinical contexts (2). Whether any of these agents will succeed in proving a tissue-agnostic efficacy, either alone or in combination, will remain an area of controversy. Generally speaking, the histology-agnostic arsenal has suffered in the past from many negative results that limited expansion beyond single-site indications (97). One important challenge is the inherent molecular resistance mechanisms that can be present locally in some tumor types. However, with a better understanding of tumor biology, combination with resistance-targeting agents or the development of second-generation therapeutics that can overcome those resistance mechanisms can hopefully lead to more tissue-agnostic approvals. Therefore, cancer drug developers should balance biological, statistical, and regulatory issues that characterize the era of molecularly driven indications, which can fast-track such change in the years to come.

Limitations

In this article, we have reported data on the clinical landscape of tissue-agnostic targets using the AACR GENIE database. GENIE contains sequencing data from multiple contributing sites that allowed a wide scale analysis of large number of samples even win tumors with

low frequency in individual sites. However, clinical data in AACR GENIE are limited especially in regard to prior treatments. Therefore, we were not able to explore possible differences between targeted therapy-naïve and pretreated populations. It is possible that some alterations could have emerged as a resistance mechanism to targeted therapeutics.

Conclusions

Current tissue-agnostic biomarkers are prevalent across multiple tumors. Drugs that target those alterations offer a broad spectrum of anticancer drug activity potentially changing the paradigm of cancer management from site-focused to genetic-focused care. Further analysis of cooccurring alterations and their impact on response to targeted therapies is warranted, in order to tailor precision treatments for patients harboring these alterations.

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