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Tumor Agnostic Therapies, a Challenge or an Opportunity?

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ABSTRACT

The concept of Tumor Agnostic Therapies (TAT) emerged from the observation that a single drug can be effective across multiple tumor locations and histological types if they share the same mutation or biomarker, as demonstrated in basket trials. This approach shifts the therapeutic target to the mutation, independent of the tumor location. The primary challenge of TAT is the heterogeneity of supporting studies, often attributed to small population sizes. This review details the molecular basis for each established agnostic biomarker and its corresponding FDA-approved therapies, focusing on product presentation, dosage, and main side effects.

Keywords: Mutation; Biomarker; Agnostic; Approval

Abbreviations: TAT: Tumor Agnostic Treatment; MSS: Microsatellite Stable; CGP: Comprehensive Genomic Profiling; ICIs: Immune Checkpoint Inhibitors; NTRK: Neurotrophic Tropomyosin Kinase Receptors; ALK: Anaplastic Lymphoma Kinase; ORR: Overall Response Rate; TMR: Tumor Mutation Burden; KRAS: Kristen Rat Sarcoma Virus; ALK: Anaplastic Lymphoma Kinase; ESMO: European Society for Medical Oncology; ETAC-S: ESMO Tumour Agnostic Classifier and Screener; MSI: Microsatellite Instability

Introduction

Traditionally, cancer treatments are based on the tissue type where the tumor originates. This historical approach resulted in different cancers requiring distinct treatments, often leaving patients with rare or treatment-resistant cancers with limited or no therapeutic options [1]. Gradually, it was observed that a single drug could be approved for multiple cancer types if they shared the same genetic mutation or biomarker. Basket trials illustrate this transition, having been extensively utilized to examine the effects of a singular drug on a specific mutation across various cancer types [2-4]. An extensive real-world analysis by Sledge et al. of nearly 300,000 molecularly profiled tumors revealed that 21.5% of these tumors possess at least one tissue-agnostic indication [5,6]. Because of the vast expansion of precision oncology, two major trends have emerged in cancer research: combination therapies and Tumor Agnostic Treatment (TAT) [7]. TAT shifts the therapeutic focus from anatomical classification to biomolecular drivers [8]. Pembrolizumab made history in 2017 [9-12] as the first tissue-agnostic therapy to receive accelerated FDA approval for MSI-H/dMMR solid tumors. Currently, the FDA has approved nine TATs across several categories, as summarized in Figure 1 [5,13].

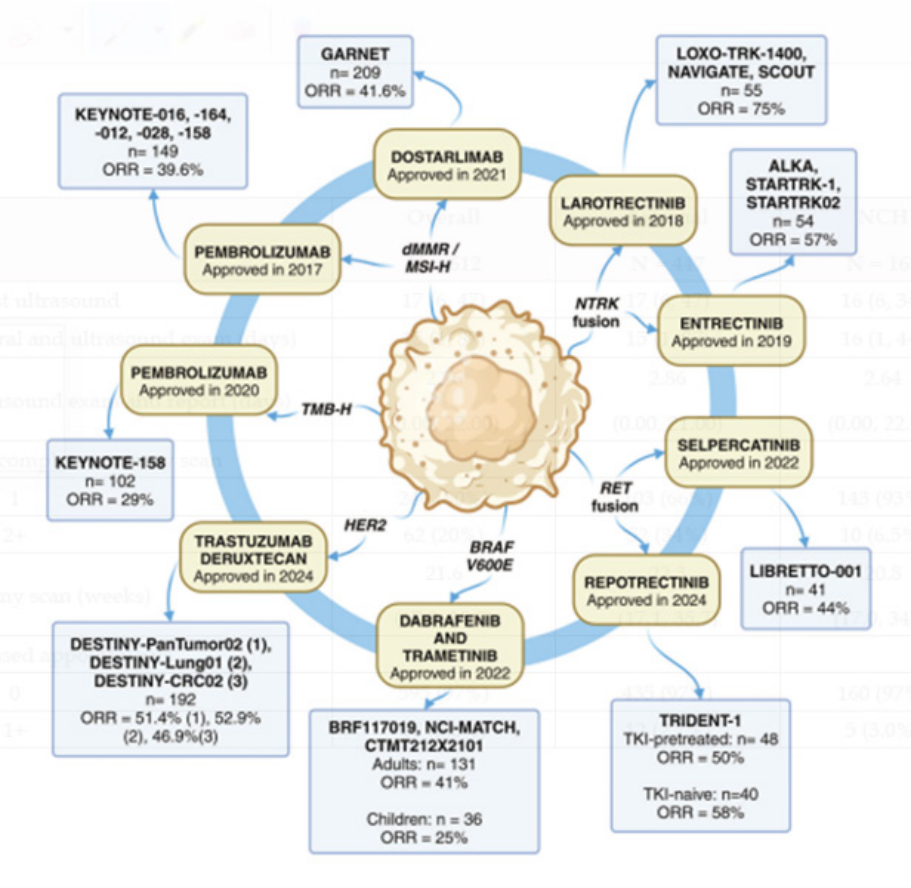

Figure 1: Main Tumor Agnostic Treatments Approved in 2025 [1].

Many Challenges in TAT

The benefit assessment of TAT presents stakeholders with various challenges. Crucially, Cureus does not allow bullet points in the body text. These challenges include:

1. A notable absence of direct comparative studies;
2. A lack of robust and accurate biomarker testing necessary to identify eligible patients;
3. The rarity of some molecular alterations targeted by agnostic therapies, which makes it challenging to recruit a sufficient number of patients;
4. The inherent heterogeneity of basket studies and the resulting infeasibility of conducting randomized clinical trials; and
5. Insufficient statistical power, as small sample sizes diminish the significance of the endpoints [14,15].

Delays in translating tumor-agnostic therapies to clinical practice stem from uncertain patient benefit due to the rarity of these mutations, which contributes to tumor heterogeneity and necessitates large trials to definitively prove effectiveness. Health technology assessment organizations are also articulating difficulties in evaluating tumor-agnostic therapies based on the clinical trial evidence submitted by drug manufacturers [16,17].

Agnostic Biomarkers

Technological advances have revealed that molecular mechanisms are responsible for the behavior of cancer cells. Agnostic biomarkers are specific molecular changes that can be targeted by therapeutic interventions irrespective of the tumor's location or histology [18]. This approach represents the novel frontier of precision medicine, rapidly evolving and revolutionizing the therapeutic landscape of tumors [19]. Many biomarkers have been approved (Table 1), offering new opportunities for organ-preserving treatment capable of downstaging locally advanced or metastatic tumors and for achieving complete or near-complete remission in early stages [20].

Table 1: FDA approved agnostic biomarkers and agnostic therapy.

Target	Mechanism	Indication	FDA approval
MSI/dMMR	PD-1 inhibition	Pembrolizumab (MSI/dMMR solid tumors) Dostarlimab (MSI/dMMR solid tumors)	23-05-2017 17-08-2021
NTRK fusion	Pan-TRK inhibition Pan-TRK, ROS1, ALK inhibition	Larotrectinib (NTRK fusion-positive solid tumors) Entrectinib (NTRK fusion-positive solid tumors and NSCLC with ROS-1 alterations) Repotrectinib (NTRK fusion positive solid tumors)	26-11-2018 15-08-2019 13-06-2024
Tumor mutation burden	PD-1 inhibition BRAF + MEK inhibition	Pembrolizumab (unresectable or metastatic TMB-H (≥ 10 mut/Mb) solid tumors) Dabrafenib + Trametinib (Patients with BRAFV600E mutated tumors)	15-06-2020 22-06-2022
REF fusion	RET inhibition	Selpercatinib (patients with RET fusion-positive tumors)	21-09-2022
HER2	HER2 inhibition	Trastuzumab-deruxtecan	5/4/2024

dMMR: mismatch repair defect, NSCLC: non-small cell lung cancer, MSI: microsatellite instability, PD-1: programmed cell death protein, ROS: reactive oxygen species, ALK: anaplastic lymphoma kinase, TRK: tropomyosin receptor kinase, BRAF: **v-**Raf murine sarcoma viral oncogene homolog B, MEK: mitogen-activated protein kinase, RET: rearranged during transfection, HER2: human epidermal growth factor 2

Microsatellite Instability (MSI)

MSI is defined as a high number of mutations in microsatellites caused by a defect in the cell's DNA mismatch repair (MMR) system; it indicates DNA stability in tumors [21]. It was the first reported agnostic biomarker [22,23]. High-frequency MSI (MSI-H/dMMR) status is a crucial factor in determining patient eligibility for immune checkpoint inhibitors (ICIs). The MSI status is assessed by next-generation sequencing (NGS) or through liquid biopsy-based comprehensive genomic profiling (CGP) [24].

Pembrolizumab: This immune checkpoint inhibitor is a highly effective treatment for MSI-H or dMMR solid tumors, while its effectiveness is limited in microsatellite stable (MSS) tumors, making the MSI status a crucial factor in determining treatment eligibility. Pembrolizumab was the first established TAT to receive FDA approval in 2017 [13,25-28].

Dostarlimab: In a Phase II trial of Dostarlimab, investigators reported a 100% rate of clinical complete response in 12 patients with MSI-H locally advanced rectal cancer. These results were further confirmed in 49 patients with MSI-high rectal cancer and 54 patients with non-rectal MSI-high locally advanced solid tumors. This led to Dostarlimab becoming a treatment option in these patients, and the FDA granted it breakthrough therapy designation [29-31].

Neurotrophic Tyrosine Receptor Kinase (NTRK) Fusion

The family of neurotrophic tropomyosin kinase receptors (NTRK or TRK) is a part of transmembrane tyrosine kinases responsible for neural development [32]. There are three members of this receptor family (TRK A, B, and C), encoded by the NTRK1, NTRK2, and NTRK3 genes. NTRK fusion, detectable by immunohistochemistry, FISH, and NGS, is more common in rare cancers, with a prevalence <5% of all cancers. This gene rearrangement leads to cancer cell transformation [32-35].

Larotrectinib: This first-in-class, orally administered, potent, and highly selective inhibitor was FDA-approved for tumor-agnostic use with TRK fusion cancers. It has shown durable responses, extended survival (five-year OS 76%, 95% CI: 65-86), and a favorable safety profile across two studies (LOXO-TRK-14001 and NAVIGATE) [35-37].

Entrectinib: A first-generation pan-TRK inhibitor, Entrectinib also has activity against proto-oncogene ROS1 and anaplastic lymphoma kinase (ALK). This potent, CNS-active TRK inhibitor demonstrated efficacy in patients with NTRK fusion-positive NSCLC, with a median PFS of 28 months (95% CI: 15.7-30.4) and median OS of 41.5 months in patients with BICR-assessed baseline CNS metastases [35,38].

Repotrectinib: This is a selective, highly potent, next-generation ROS1 and TRK inhibitor. On June 13, 2024, the FDA granted accelerated approval to Repotrectinib following the results of TRIDENT-1, a multicenter, single-arm, open-label trial in 88 adult patients with locally advanced or metastatic NTRK gene fusion-positive solid tumors (TKI pretreated or naïve). Confirmed overall response rate (ORR) was 58\% (95% CI: 41-73) in the naïve group versus 50% (95\% CI: 35-65) in the pretreated group, demonstrating durable clinical activity [38-41].

Tumor Mutation Burden

(TMB) defined as the total number of mutations per megabase found in the DNA of cancer cells, it is used as a biomarker to predict patient's response to immune checkpoint inhibitors [42], because mutations lead to more neoantigens that the immune system can rec-

ognize and attack, the results confirmed that a high TMB is linked to better responses of Pembrolizumab in lung cancer [43,44], and melanoma [45,46], however, findings for breast and prostate cancers are inconsistent, real-world analysis suggest that TMB≥10 is a reasonable cut-off [47-50].

BRAF V600E Mutation

The v-Raf murine sarcoma viral oncogene homolog B V600E mutation is a genetic alteration that results in an overactive BRAF protein. This protein sends continuous growth signals to cells, leading to uncontrolled cell proliferation. It is most commonly observed in thyroid cancers (51%) and melanomas (19%). The combination of Dabrafenib (a RAF inhibitor) and Trametinib (a MEK inhibitor) inhibits MAPK/ERK signaling at two different points [51]. They were initially approved for BRAF-mutated melanoma [52]. Data from the ROAR trial and NCI-MATCH subprotocol HG [53,54] led to the FDA approval of this combination for BRAF V600E-mutated pretreated solid tumors [55].

Rearranged During Transfection (RET) Fusion

This refers to the use of selective RET inhibitors like Selpercatinib to treat various cancers that share a common RET gene fusion. The LIBRETTO-001, an ongoing Phase 1/2 trial, demonstrated an objective response rate (ORR) of 43.9% (95% CI: 28.5-60.3) as per the independent review committee [56,57].

HER2 Overexpression

Overexpression of HER2 is now a target of TAT in certain solid tumors [58,59]. Trastuzumab-deruxtecan (T-DXd) is a human epidermal growth factor 2 (HER2)-directed antibody-drug conjugate that received approval based on clinically meaningful benefit: a 37.1% (95% CI: 31.3-43.2) overall response rate (ORR) across different tumor cohorts. Median OS was 13.4 months (95% CI: 11.9-15.5). These data support the potential role of T-DXd as a tumor-agnostic therapy for patients with HER2-expressing solid tumors [60-63].

Main Characteristics of Agnostic Treatments

Nine products are currently approved in this category of therapy, encompassing three main drug classes: targeted therapy, immunotherapy, and antibody-drug conjugates. While these agnostic treatments are certainly much more easily administered and better tolerated than traditional chemotherapy, they still present a range of different and variable adverse events capable of affecting a person's quality of life and overall well-being. Healthcare professionals must be aware of these effects to prevent and manage them in early stages [64,65]. Specific management strategies are implemented for common side effects (Table 2). For fatigue or the deeper state of asthenia, physical therapy and cognitive behavioral therapy are recommended. Skin reactions are managed with specialized creams, UV protection, and advising patients to avoid excessive washing. Gastrointestinal disorders require careful hydration, dietary advice (food warnings), and anti-diarrheal or anti-emetic medication. For endocrine disorders or serious adverse events related to immunotherapy, corticosteroids or even immunosuppressants are usually administered. Furthermore, more serious side effects, including cardiac dysfunction, interstitial lung disease, and liver problems, are monitored from baseline to ensure early identification; these complications often necessitate hospitalization and adequate management. Finally, diligent monitoring of side effects ensures treatment compliance, and maintaining vigilance is necessary even after treatment is stopped [66-72].

Table 2: Pharmacological Characteristics of TAT [69-72].

Drug	Target	Form	Posology	Common adverse events
Pembrolizumab	PD-1	solution 100 mg 200 mg IV SC	200 mg / 3 weeks or 400 mg / 6 weeks or 2 mg/kg / 3 weeks	fatigue, pain in muscles, joint or bone rash, diarrhea, fever, cough, decreased appetite, itching, shortness of breath, constipation, nausea, hypothyroidism
Dostarlimab	PD-1	solution IV use 500 mg	500 mg/3 weeks (4 doses) then 1000 mg /6 weeks	fatigue/asthenia, anemia, rash, nausea, diarrhea, constipation, and vomiting
Larotrectinib	NTRK	Oral route caps 25 mg 100 mg	100 mg twice daily	fatigue, nausea, dizziness, vomiting, increased AST, ALT, cough, constipation and diarrhea
Entrectinib	NTRK	caps 100 mg 200 mg	600 mg once daily	fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders
Dabrafenib + Trametinib	BRAF + MEK	D : caps 50 mg, 75 mg T : tablets 2mg	D: 150 mg twice daily + T: 2 mg once daily	pyrexia, fatigue, chills, peripheral edema, nausea, constipation, vomiting, diarrhea, rash, headache, hemorrhage, cough, myalgia, and arthralgia
Selpercatinib	RET	caps 40 mg 80 mg	< 50 kg 120 mg twice daily ≥ 50 kg 160 mg twice daily	hypertension, prolonged QT interval, diarrhea, dyspnea, fatigue, abdominal pain, hemorrhage, headache, rash, constipation, nausea, vomiting, and edema
Trastuzumab-deruxtecan	HER 2	powder for concentrate for solution for IV infusion 100 mg	5.4 mg / kg of body weight / 3 weeks	nausea, vomiting, diarrhea, constipation, fatigue, decreased appetite, alopecia, and anemia, interstitial lung disease, decreased ventricular ejection fraction

Emerging Tumor Agnostic Treatments

Other agnostic treatment candidates are currently under investigation and showing promise, as these drugs demonstrate the ability to shrink tumors in patients with various types of genetic disorders. These candidates include several distinct targets:

- Therapies targeting the Kristen Rat Sarcoma Virus (KRAS), such as Adagrasib, which showed promising activity in patients with advanced solid tumors during the Krystal-1 trial [73].
- Anaplastic Lymphoma Kinase (ALK) inhibitors, for which current data suggest tissue-agnostic activity in neoplasms bearing ALK fusions or rearrangements [74,75].
- Neuroregulin 1 (NRG1), an epidermal growth factor, is being evaluated with zenocotuzumab in patients with NRG1 fusion-positive tumors in the eNRGy trial [76,77]; trials targeting BRAF non-V600 mutations [78] also appear interesting.
- Agents targeting Homologous Recombination Deficiency (e.g., BRCA mutation), where the tumor-agnostic (BRCA1/2) evaluation has shown significant clinical impact, although further tools and validation trials are still needed [79, 80].

To assist and optimize drug development in this area, the European Society for Medical Oncology (ESMO) Precision Medicine Working Group, together with a multidisciplinary team of international experts, recently developed the ESMO Tumour Agnostic Classifier and Screener (ETAC-S). This tool is designed for assessing the tumor-agnostic potential of molecularly guided therapies. This growing acknowledgment of the tumor-agnostic approach is encouraging the development of such treatments to meet the needs of patients with less frequent cancers [81-83].

Conclusion

With the six tissue-agnostic biomarkers and nine corresponding therapies currently approved, Tumor Agnostic Therapy (TAT) is an area of active research and development. Further gene targets, including the ALK, KRAS, and ROS1 genes, are actively being explored. “Basket” trials remain the most suitable study type for TAT, as they allow for the recruitment of patients with many tumor types. Challenges associated with basket trials are encouraging the development of adaptive clinical trial designs to establish suitable evidence requirements for targeted treatments used in smaller, more specific patient subgroups and allow for reassessment as more evidence emerges. Finally, collaborative approaches, such as the ESMO Tumour Agnostic Classifier and Screener (ETAC-S), are needed among health professionals to increase awareness of when and where it is appropriate to use TAT and other precision medicine treatments.

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