

Tissue-Agnostic Cancer Therapy Approvals



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KEYWORDS

- Tissue-agnostic • Selpercatinib • Dabrafenib • Trametinib • Pembrolizumab
- Dostarlimab • Entrectinib • Larotrectinib

KEY POINTS

- Tissue-agnostic cancer therapy has been transformative in the way we manage cancer.
- Cancers of different origins with shared biomarkers can be treated with personalized matched therapies independent of histology.
- To date, multiple drugs/regimens have received Food and Drug Administration approval in a tissue-agnostic indication for patients with advanced cancers.
- Early pilot studies have shown the potential benefit of neoadjuvant approaches with tissue-agnostic therapies.

INTRODUCTION

Tissue-agnostic cancer therapy represents a revolutionary paradigm shift in the field of precision oncology. Unlike traditional cancer treatments that primarily target specific tumor types based on their origin (eg, breast cancer, lung cancer, renal cell cancer, etc), tissue-agnostic therapies are histology-independent and focus on the genetic and molecular characteristics of tumors, irrespective of their tissue of origin. This innovative approach offers new hope to cancer patients, as it recognizes that the same genetic aberrations can drive cancer in multiple tissues and locations throughout the body. Over the past few years, several biomarker-driven therapeutics with pan-cancer tissue-agnostic efficacy have been evaluated in clinical trials and approved by the US Food and Drug Administration (FDA)¹ and the European Medicines Agency (EMA). Such drugs or regimens can be administered to patients with advanced solid tumors regardless of tissue of origin, which represents an evolutionary advance from tumor site-specific therapies that have been standard of care for decades. Those approvals provide alternative

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options for patients with advanced cancers and are paradigm shifters, especially in the context of rare malignancies or those that lack effective treatment options.²

To date, six drugs/regimens have been approved by the US FDA for use in patients with all solid tumors which harbor one of five biomarkers.^{3–9} Herein, we review the current landscape of those tissue-agnostic cancer therapies and elaborate on relevant clinical information which can help surgical oncologists to understand better about those therapies.

CURRENT APPROVALS

The US FDA has approved six drugs/regimens for use in a tissue-agnostic manner (Fig. 1). Those include larotrectinib or entrectinib in patients with *NTRK* fusions, dabrafenib plus trametinib in patients with *BRAF* V600E mutations, seliprecatinib in patients with *RET* fusions, pembrolizumab in patients with high tumor mutation burden (TMB) or deficient mismatch repair (dMMR), and dostarlimab in patients with dMMR. In the following sections, we will elaborate on each of those approved drugs/regimens from a clinical perspective, recognizing that with improved therapeutic potential, patients previously believed to be biologically or technically unresectable (or borderline resection) may have new options that can allow for multimodal treatment.

DABRAFENIB PLUS TRAMETINIB

Dabrafenib is an inhibitor of BRAF and trametinib is a MEK inhibitor, which when combined together lead to synergistic activity blocking aberrant BRAF signaling.¹⁰

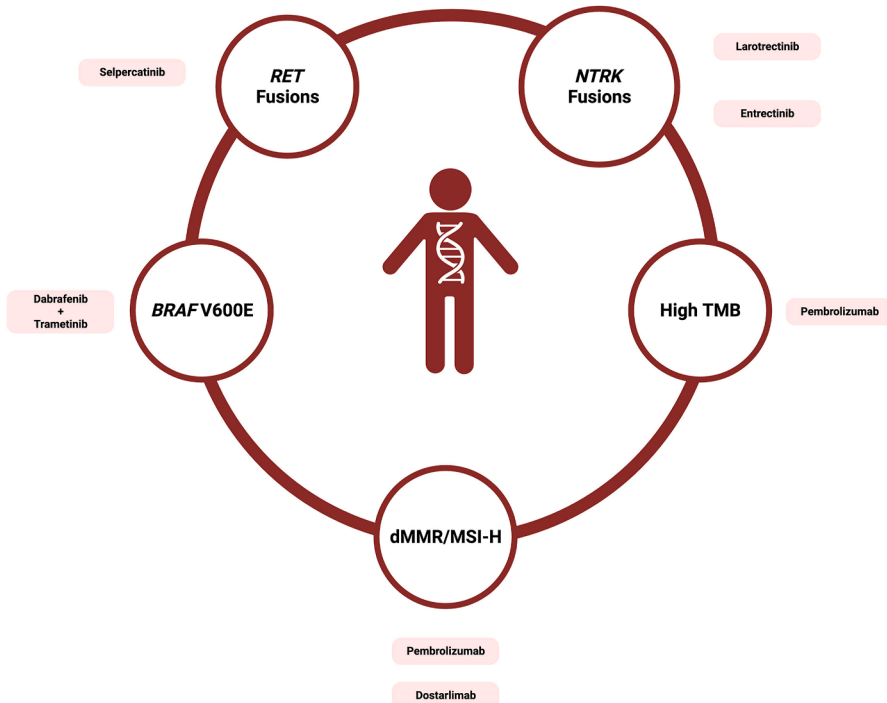


Fig. 1. Currently approved tissue-agnostic targets. (Used with permission from Prof. Vivek Subbiah, MD. Created with BioRender.)

Dabrafenib plus trametinib combination is currently approved by the US FDA for the treatment of patients with advanced unresectable or metastatic solid tumors whose tumors harbor *BRAF* V600E mutations and have progressed following prior treatment with no satisfactory alternative treatment options, with the exception of patients with colorectal cancer (CRC) as discussed in a later section.^{4,5} In addition to its tissue-agnostic indication, dabrafenib plus trametinib combination is approved in multiple other disease-specific indications including melanoma, non-small-cell lung cancer (NSCLC), anaplastic thyroid cancer (ATC), and pediatric low-grade glioma (LGG) (Table 1).

Alteration of Interest

BRAF V600E is a MAPK pathway pathogenic alteration that leads to uncontrolled cellular growth and differentiation which is independent on upstream activation.^{11,12} A prior study suggested that *BRAF* V600E is present in nearly 3% of patients in the American Association for Cancer Research (AACR) GENIE (Genomics Evidence Neoplasia Information Exchange) database pan-cancer cohort. The highest frequency of *BRAF* V600E mutation was observed in patients with thyroid cancer (40.2%), melanoma (20.3%), histiocytosis (17.3%), and CRC (7.9%). A long list of other tumor types that harbored *BRAF* V600E mutations was identified by investigators suggesting that *BRAF* V600E mutations are not infrequent.²

Detection of Biomarker

BRAF V600E can be detected using immunohistochemistry, polymerase chain reaction (PCR)-based technologies, and sequencing-based technologies including sanger sequencing and next-generation sequencing (NGS).^{13–15} Each method will have its own advantages and disadvantages; cost-effectiveness may also play a role in assay selection especially in low-resource settings. Nevertheless, patients with advanced solid tumors should be tested for *BRAF* V600E, as such testing may confer sensitivity to a targeted therapeutic option, especially at the time of progression.^{10,16}

Clinical Evidence

Registrational studies leading to approval of dabrafenib plus trametinib combination in the tissue-agnostic indications included a pooled analysis of the Rare Oncology Agnostic Research (ROAR) basket trial (NCT02034110), National Cancer Institute's Molecular Analysis for Therapy Choice (NCI-MATCH) Arm H (NCT02465060), Study X2101 (NCT02124772), and Study G2201 (NCT02684058).^{4,5,17–20} The safety and effectiveness of this treatment were assessed in a group of 131 adult patients enrolled in 2 open-label basket trials known as BRF117019 (NCT02034110) and NCI-MATCH (NCT02465060), as well as in 36 pediatric patients participating in CTMT212 × 2101 (NCT02124772). These results were further substantiated by findings from the COMBI-d, COMBI-v, and BRF113928 studies which tested the combination in patients with melanoma and NSCLC. BRF117019 focused on adult patients with *BRAF* V600E mutation-positive solid tumors, which encompassed a range of conditions such as biliary tract cancers (ie, gallbladder cancer and intrahepatic/extrahepatic cholangiocarcinoma), adenocarcinoma of the small intestine, gastrointestinal stromal tumor, and ATC, as well as high-grade glioma (HGG) and LGG. Meanwhile, the NCI-MATCH Subprotocol H examined adult patients with *BRAF* V600E mutation-positive solid tumors, excluding melanoma, thyroid cancer, or CRC. In CTMT212 × 2101 trial, parts C and D of the study involved 36 pediatric patients with *BRAF* V600-refractory or *BRAF* V600-recurrent LGG or HGG.¹⁹ The primary measure of effectiveness in these trials was the overall response rate (ORR), evaluated using standard response criteria.

Table 1 Food and Drug Administration–approved indications for tissue-agnostic drugs as of Food and Drug Administration packaging labels on October 2023	
Dabrafenib and trametinib	• Patients with unresectable or metastatic melanoma with <i>BRAF</i> V600E or V600K mutations as detected by an FDA-approved test. • The adjuvant treatment of patients with melanoma with <i>BRAF</i> V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection. • Patients with metastatic NSCLC with <i>BRAF</i> V600E mutation as detected by an FDA-approved test. • Patients with locally advanced or metastatic anaplastic thyroid cancer with <i>BRAF</i> V600E mutation and with no satisfactory locoregional treatment options. • Adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with <i>BRAF</i> V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. • Pediatric patients 1 year of age and older with low-grade glioma with a <i>BRAF</i> V600E mutation who require systemic therapy.
Selpercatinib	• Adult patients with locally advanced or metastatic NSCLC with a <i>RET</i> gene fusion, as detected by an FDA-approved test. • Adult and pediatric patients 12 years of age and older with advanced or metastatic MTC with a <i>RET</i> mutation, as detected by an FDA-approved test, who require systemic therapy. • Adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a <i>RET</i> gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) • Adult patients with locally advanced or metastatic solid tumors with a <i>RET</i> gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.
Entrectinib	• Adult patients with ROS1-positive metastatic NSCLC as detected by an FDA-approved test. • Adult and pediatric patients older than 1 month of age with solid tumors that have a NTRK gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have progressed following treatment or have no satisfactory alternative therapy.
Larotrectinib	• Adult and pediatric patients with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments or that have progressed following treatment.
Pembrolizumab	• Melanoma ◦ For the treatment of patients with unresectable or metastatic melanoma. ◦ For the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB, IIC, or III melanoma following complete resection. • NSCLC ◦ In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations.

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Table 1
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- In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
- As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 (TPS $\geq 1\%$) as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations, and is stage III, where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic.
- As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS $\geq 1\%$) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.
- For the treatment of patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- As a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC.
- HNSCC
 - In combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
 - As a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
 - As a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
- cHL
 - For the treatment of adult patients with relapsed or refractory cHL.
 - For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.
- PMBCL
 - For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.
- Urothelial carcinoma
 - In combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.
 - As a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy, or who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy.
 - As a single agent for the treatment of patients with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

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- MSI-H or dMMR cancer
 - For the treatment of adult and pediatric patients with unresectable or MSI-H or dMMR solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- MSI-H or dMMR CRC
 - For the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC as determined by an FDA-approved test.
- Gastric cancer
 - In combination with trastuzumab, fluoropyrimidine-containing chemotherapy, and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma.
- Esophageal cancer
 - For the treatment of patients with locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1–5 cm above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either in combination with platinum-based and fluoropyrimidine-based chemotherapy, or as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test.
- Cervical cancer
 - In combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
 - As a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
- HCC
 - For the treatment of patients with HCC who have been previously treated with sorafenib.
- MCC
 - For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic MCC.
- RCC
 - In combination with axitinib, for the first-line treatment of adult patients with advanced RCC.
 - In combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
 - For the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.
- Endometrial carcinoma
 - In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

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- As a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
- **TMB-H Cancer**
 - For the treatment of adult and pediatric patients with unresectable or metastatic TMB-H (≥ 10 mutations/megabase) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- **cSCC**
 - For the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.
- **TNBC**
 - For the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
 - In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA approved test.
- **Adult classical Hodgkin lymphoma and adult primary mediastinal large b-cell lymphoma: Additional dosing regimen of 400 mg every 6 weeks**
 - For use at an additional recommended dosage of 400 mg every 6 weeks for classical Hodgkin lymphoma and primary mediastinal large b-cell lymphoma in adults.

Dostarlimab

- **Endometrial cancer**
 - In combination with carboplatin and paclitaxel, followed by dostarlimab as a single agent for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is dMMR, as determined by an FDA-approved test, or MSI-H.
 - As a single agent for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation.
- **dMMR recurrent or advanced solid tumors**
 - As a single agent for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

Abbreviations: cHL, classical Hodgkin lymphoma; CPS, combined positive score; CRC, colorectal cancer; cSCC, cutaneous squamous cell carcinoma; dMMR, mismatch repair deficient; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell cancer; MCC, Merkel cell carcinoma; MSI-H, microsatellite instability-high; MTC, medullary thyroid cancer; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed cell death-ligand 1; PMBCL, primary mediastinal large b-cell lymphoma; RCC, renal cell carcinoma; RET, rearranged during transfection; TMB-H, tumor mutational burden-high; TNBC, triple-negative breast cancer; TPS, Tumor Proportion Score.

Among the 131 adult patients, 41% (with a 95% confidence interval [CI] of 33% to 50%) achieved an objective response. The patient pool included 24 different tumor types. Notably, for specific tumor types, the ORR was 46% (95% CI: 31% to 61%) for biliary tract cancers, 33% (95% CI: 20% to 48%) for HGG (combined), and 50% (95% CI: 23% to 77%) for LGG (combined). As for the 36 pediatric patients, they achieved an ORR of 25% (95% CI: 12% to 42%). Moreover, 78% of these patients had a duration of response (DOR) lasting at least 6 months, and an impressive 44% experienced a DOR of at least 24 months. The accumulating evidence from all those studies has shown pan-cancer activity of dabrafenib plus trametinib in multiple cancer types.¹⁶ It is notable that due to low response rates to BRAF and MEK inhibitor therapy, patients with CRC harboring BRAF V600 mutation were excluded in the FDA indication. Lack of response is in part due to an adaptive/innate mechanism of resistance with epidermal growth factor receptor (EGFR) activation which can be addressed by the addition of EGFR inhibitor therapy.^{4,5,21,22} Therefore, BRAF V600 may still be actionable in CRC with the addition of cetuximab. In fact, another BRAF inhibitor (encorafenib) in combination with cetuximab is approved for CRC.²²

Side Effects

Common side effects with dabrafenib and trametinib include fatigue, fever, nausea, vomiting, diarrhea, constipation, rash, chills, headache, hemorrhage, cough, myalgia, arthralgia, and edema. Less frequent but more serious side effects include secondary malignancies, gastrointestinal perforation, venous thromboembolic events, cardiomyopathy, ocular toxicities, pneumonitis, serious febrile reactions, hyperglycemia, and hemophagocytic lymphohistiocytosis.^{4,5} Management with preventive measures, supportive care, and treatment modification might be warranted given the high rates of adverse events with combination therapy.¹⁶

Dosage

In adult patients, dabrafenib is approved for use at a dose of 150 mg orally twice daily while trametinib is approved at a dose of 2 mg orally once daily. Both drugs should be taken at the same time each day at least 1 hour before or 2 hours after a meal.^{4,5} In pediatrics, dosing should be based on body weight, and oral suspension formulations are available.^{4,5} Dosing modifications maybe necessary as guided by possible toxicities.¹⁶

SELPERCATINIB

Selpercatinib is a highly potent selective RET inhibitor that is currently approved by the US FDA for treatment of patients with advanced solid tumors with *RET* fusions who have progressed on or following prior systemic therapy or have no satisfactory alternative treatment options. In addition to its tissue-agnostic indication, selpercatinib is approved in patients with advanced NSCLC and *RET* fusion, medullary thyroid carcinoma with *RET* mutation, and advanced thyroid cancer with *RET* fusion (see [Table 1](#)).^{3,23,24}

Alteration of Interest

RET fusions are chromosomal rearrangement of the *RET* gene which have been suggested to drive oncogenesis in a variety of tumor types.^{25–30} In a prior study, *RET* fusions were identified in 1.5% of samples that were tested for structural variants and only 0.3% of the pan-cancer cohort, which highlights the importance of testing on identification of an important biomarker. *RET* fusions were most common in patients with thyroid cancer (36%) and NSCLC (5.7%), among other cancer types.²

Detection of Biomarker

RET fusions can be detected using immunohistochemistry, PCR-based technologies, or NGS-based technologies.^{31–40} Multiple factors including cost-effectiveness, assay's sensitivity and/or specificity, and the ability to detect fusion partner may weigh in while deciding the optimum diagnostic method.⁴¹ Nevertheless, patients with advanced solid tumors should be tested for *RET* fusions as such testing may confer sensitivity to a targeted therapeutic option, especially at the time of progression.

Clinical Evidence

LIBRETTO-001 (NCT03157128) was the registrational study leading to tissue-agnostic approval of selpercatinib.^{3,42} The study was a multi-cohort study that showed pan-cancer efficacy of selpercatinib consistent with initial positive results seen in patients with *RET* fusion positive thyroid cancer and NSCLC.^{42–45} The ORR was 61% in previously treated NSCLC, 84% in treatment-naïve NSCLC, 79% in previously treated thyroid cancer, and 100% in treatment-naïve thyroid cancer.³ The ORR in cancers other than lung and thyroid was 44%. Among the tumor types enrolled, the ORR in tumor types reported included pancreatic cancer (n = 11; 55%), CRC (n = 10; 20%), and salivary gland (n = 4, 50%), among others.⁴²

Side Effects

Common side effects with selpercatinib include nausea, diarrhea, constipation, edema, fatigue, dry mouth, hypertension, abdominal pain, rash, and headache. Less frequent but more serious side effects include hepatotoxicity, pneumonitis, QT interval prolongation, hemorrhagic events, hypersensitivity, tumor lysis syndrome, impaired wound healing, and hypothyroidism.³ Recommendations for management of adverse events related to selective *RET* inhibitors, including selpercatinib, have been published.⁴⁶

Dosage

Selpercatinib is approved for use at a dose of 160 mg orally twice daily in patients 50 kg or greater and 120 mg orally twice daily in patients less than 50 kg. Specific dose modifications might be necessary especially in patients with severe hepatic impairment.³

ENTRECTINIB

Entrectinib is a multikinase inhibitor with primary activity against TRK, ROS1, and ALK.⁴⁷ Entrectinib is currently FDA approved for adult and pediatric patients with advanced or metastatic solid tumors that harbor *NTRK* gene fusion, which have progressed following treatment or have no satisfactory alternative therapy.⁹ In addition, disease-specific indication is approved in patients with NSCLC with tumors positive for ROS1 (see [Table 1](#)).

Alteration of Interest

NTRK fusions result from chromosomal rearrangement between one of the *NTRK* genes (*NTRK1*, *NTRK2*, or *NTRK3*) and a second gene, resulting in aberrant activation signal that leads to promotion of cellular growth and survival.^{48–50} *NTRK* fusions are estimated to be present in nearly 1.6% of cancer specimens based on an analysis of a pan-cancer cohort in the AACR GENIE database.² The highest frequency of *NTRK* fusions was observed in thyroid cancer (n = 46; 17.2%) and salivary gland cancer (n = 29; 15.3%), among other cancers.²

Detection of Biomarker

Similar to *RET* fusions, different technologies are available for the detection of *NTRK* fusions including immunohistochemistry, fluorescence in situ hybridization, PCR-based technologies, and NGS-based technologies. Several factors may help to select the optimum approach including assay's availability, cost, turnaround time, and analytical characteristics.⁵¹ Regardless of the method, it is important to emphasize the need to test patients with advanced solid tumors to *NTRK* fusions as those may confer sensitivity to approved TRK inhibitors.

Clinical Evidence

Data on tissue agnostic-activity of entrectinib in adults come from a pooled analysis of 3 phase 1-2 trials: ALKA-372 to 001, STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267); while in pediatrics, data originate from STARTRK-NG (NCT02650401) and TAPISTRY (NCT04589845) trials.^{9,52} Given the relatively high and durable response rate (ORR of 59% in adults and 70% in children) which was seen in patients with multiple tumor types including brain tumors and infantile fibrosarcoma, entrectinib is currently approved for patients with advanced solid tumors regardless of histology.⁹

Side Effects

The most common side effects observed with entrectinib are fatigue, nausea, vomiting, diarrhea, constipation, dysgeusia, edema, dizziness, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, pyrexia, arthralgia, and vision problems. Other less frequent but serious side effects include congestive heart failure, central nervous system (CNS) side effects, skeletal fractures, hepatotoxicity, hyperuricemia, and QT prolongation.⁹

Dosage

The currently approved dose of entrectinib is 600 mg orally once daily in adult patients while age-specific and body weight-specific dosing may be required in pediatrics.⁹ Dosing modifications may be required in cases of toxicities.

LAROTRECTINIB

Larotrectinib is another small-molecule tyrosine kinase inhibitor with activity against TRK. It is currently approved for treatment of patients with advanced solid tumors which have *NTRK* gene fusion without a known resistance mutation who have progressed after prior therapy or have no satisfactory alternative treatment options.⁸

Alteration of Interest and Biomarker Detection

As discussed in the section on entrectinib, *NTRK* fusions are estimated to be prevalent in nearly 1.6% of patients with cancer. Variable methods for detection are available with different advantages and disadvantages, although testing should be done in all patients with solid tumors.^{2,51}

Clinical Evidence

The pan-cancer efficacy of larotrectinib has been demonstrated in LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431) trials. With an ORR of 75% in a pooled analysis of 55 patients with *NTRK* fusions, the FDA issued approval for the use of larotrectinib in patients with advanced solid tumors.^{53,54} Intracranial activity has also been reported.

Side Effects

The most common side effects observed with larotrectinib are increased aspartate transaminase, increased alanine transaminase, increased alkaline phosphatase, anemia, leukopenia, neutropenia, lymphopenia, musculoskeletal pain, fatigue, hypoalbuminemia, cough, constipation, diarrhea, dizziness, hypocalcemia, nausea, vomiting, pyrexia, and abdominal pain. Less frequent but possibly serious side effects include CNS adverse reactions and skeletal fractures.⁸

Dosage

The recommended dose of larotrectinib is 100 mg orally twice daily. In patients with a body surface of less than 1 m², the dose should be adjusted to 100 mg/m² orally twice daily. Dose adjustment may be needed in case of toxicity.⁸

PEMBROLIZUMAB

Pembrolizumab is a monoclonal anti-programmed death receptor-1 (PD-1) antibody which blocks interaction between PD-1 receptor and PD-L1 ligand normally leading to the suppression of T-cell function; hence, enhancing immune response against cancer cells.⁵⁵ Pembrolizumab is currently approved for multiple disease indications including melanoma, NSCLC, head and neck squamous cell carcinoma, classic Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, CRC, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma (HCC), Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, cutaneous squamous cell carcinoma, and triple-negative breast cancer (see [Table 1](#)). In addition, it is currently the only drug regimen with 2 tissue-agnostic indications in patients with advanced solid tumors. These include tumors with high TMB defined as greater than 10 mutations per megabase of DNA or microsatellite instability-high (MSI-H)/dMMR status.⁶

Alterations of Interest

TMB is a reflection of the magnitude of genomic instability defined by burden of mutation across the genome. Data suggest that tumors with high burden of mutations may respond better to therapies activating the immune system.⁵⁶ In a pan-cancer cohort, 20.3% of samples had high TMB status (defined as ≥ 10 mutations per megabase which is the current cutoff used for pembrolizumab tissue-agnostic approval). Cancers with highest frequency of high-TMB status are melanoma (49.1%), bladder cancer (38.8%), non-melanoma skin cancer (36.9%), small-cell lung cancer (35.8%), and small bowel cancer (35.3%), among other cancers.²

Mismatch repair (MMR) is a process for repair of DNA damage that maintains genomic integrity. Cancers deficient in MMR accumulate genetic mutations which can drive oncogenesis and associate with poor prognosis. Such hypermutational status and dMMR can also lead to missed correction of repeated multinucleotide sequences, also called microsatellites which have been implicated in the development of cancer.^{57,58} It is estimated that MSI-H status is present in nearly 3% of pan-cancer samples according to meta-analysis data.⁵⁹ Highest frequencies are expected in patients with endometrial cancer and gastrointestinal cancers.^{58,59}

Detection of Biomarker

TMB status can be identified based on a calculation of the number of mutations per megabase as detected in NGS. Cutoffs used for defining high, intermediate, and low status vary, although the pembrolizumab approval was based on data suggesting

that tumors with TMB of 10 or more would show favorable response to treatment with immunotherapy.^{6,56,60,61}

MSI/MMR status can be detected using either testing for relevant genetic alterations in MMR genes (eg, *MSH2*, *MLH1*, *PMS2*, and *MSH6*) via NGS, although complex, or, more commonly, indirect detection of protein expression using immunohistochemistry or PCR-based detection. Other methods may be available although less frequently applied in clinical practice.^{57,62,63}

Clinical Evidence

The pan-cancer efficacy of pembrolizumab in patients with TMB high cancers was demonstrated based on data from the KEYNOTE-158 trial (NCT02628067) which showed an ORR of 29% across multiple tumor types when using cutoff of 10 mutations per megabase. Similarly, the pan-cancer efficacy of pembrolizumab in patients with MSI-H/dMMR cancers was demonstrated based on data from multiple trials including KEYNOTE-164 (NCT02460198), KEYNOTE-158 (NCT02628067), and KEYNOTE-051 (NCT02332668). The ORR in pooled analysis was 33.3% with a median DOR of 63.2 months.⁶

Side Effects

The most common side effects observed with pembrolizumab monotherapy are fatigue, musculoskeletal pain, rash, pruritis, nausea, diarrhea, constipation, pyrexia, dyspnea, cough, decreased appetite, pain including abdominal pain, and hypothyroidism. Guidelines for management of immune-related adverse events have been published by different societies.^{64–66}

Dosage

Pembrolizumab is given in intravenous infusion of 200 mg every 3 weeks or 400 mg every 6 weeks. In pediatric patients with TMB-high cancers, the dose is 2 mg/kg (up to 200 mg) every 3 weeks.⁶ Dosing modifications might be needed.

DOSTARLIMAB

Dostarlimab is an anti-PD-1 monoclonal antibody that promotes immune response against cancer cells by blocking the PD-1/PD-L1 interaction.⁶⁷ Dostarlimab is currently approved as a single agent for treatment of adult patients who have dMMR recurrent or advanced solid tumors which have progressed after prior therapy and have no alternative satisfactory treatment options. In addition to its tissue-agnostic indication, dostarlimab have a disease-specific indication for patients with advanced dMMR endometrial cancer⁷ (see [Table 1](#)).

Alteration of Interest and Detection of Biomarker

As discussed with pembrolizumab, the most common methods for detection of dMMR status are immunohistochemistry and PCR. Other methods may be available although less established.^{57,62,63}

Clinical Evidence

The pan-cancer efficacy of dostarlimab was demonstrated as part of the GARNET trial (NCT02715284) which showed an ORR of 41.6% in 209 patients with advanced solid tumors that had dMMR.^{7,68}

Side Effects

The most common side effects observed with dostarlimab are fatigue, anemia, diarrhea, and nausea. Immune-mediated side effects have been reported, and guidelines exist for their management.^{64–66}

Dosage

The current approved dose for dostarlimab is 500 mg every 3 weeks for 4 doses followed by 1000 mg every 6 weeks given as intravenous infusion over 30 minutes.⁷ Dosing modifications might be needed in patients with toxicities.

EMERGING TISSUE-AGNOSTIC THERAPIES

The current approvals only represent the beginning of the revolution in tissue-agnostic precision therapies for cancer. For example, promising pan-cancer efficacy data were reported recently with adagrasib in patients with *KRAS* G12C cancers.⁶⁹ Similarly, erdafitinib showed responses across 16 distinct tumor types with *FGFR* alterations.⁷⁰ Trastuzumab deruxtecan showed tissue-agnostic activity in patients with HER2-overexpressing tumors.⁷¹ In addition, zenocutuzumab showed activity across patients with different types of *NRG* fusion positive cancers.⁷² *TP53* Y220 C mutations appear as a possible additional tissue-agnostic target with responses seen with PC14586, a small molecule corrector of Y220 C mutant p53.⁷³ *ALK* fusions are also potentially tissue-agnostic targets given cumulative evidence from multiple trials with *ALK* inhibitors⁷⁴

Belzutifan, a hypoxia-inducible factor inhibitor, was approved in adult patients with germline von Hippel-Lindau (VHL)–driven positive malignancies that could arguably be called tumor agnostic in the germline setting.⁷⁵ VHL disease is known to be linked with the development of both benign and malignant neoplasms, encompassing conditions such as clear-cell renal cell carcinoma, pancreatic neuroendocrine tumors, as well as hemangioblastomas found in the CNS and retina. In addition, pemigatinib has been approved for *FGFR1*-rearranged myeloid neoplasms which is a hematological tissue-agnostic targeted therapy.^{76,77}

SURGICAL CONSIDERATIONS

As highlighted in prior sections, some complications of tissue-agnostic therapies may require surgical interventions (eg, perforations and skeletal fractures). Those complications should be managed according to standard surgical management algorithms given the lack of specific recommendations.

Wound healing may be a concern during the use of dabrafenib/trametinib combination or selipercatinib due to the antiangiogenic effects of trametinib and/or selipercatinib. The recommendation for selipercatinib is to hold the drug for 5 to 7 days prior to and 2 weeks after a planned major surgical procedure.⁴⁶ In the case of dabrafenib/trametinib, trametinib may need to be held 5 to 7 days prior to surgery while dabrafenib can be continued until the day of surgery.⁷⁸

NEOADJUVANT USE OF TISSUE-AGNOSTIC THERAPIES

The use of tissue-agnostic therapies in the neoadjuvant setting might have a compelling rationale. Primarily, immunotherapy fosters a more robust immune response against a diverse array of antigens, enhancing the tumor-antigen load. Its efficacy is heightened by circumventing immunosuppression, preventing potential impediments such as postsurgical glucocorticoid secretion, which may otherwise compromise

immune cell dynamics.⁷⁹ The intact structure of the lymphatic system under neoadjuvant conditions facilitates superior interaction between immune cells and the tumor microenvironment. Moreover, neoadjuvant immunotherapy proves cost-effective with fewer doses required, diminishing the possibility of resistance due to limited exposure. Its patient-friendly regimen enhances compliance, and it serves as a platform for biomarker development and a deeper comprehension of the underlying mechanisms of action, marking a paradigm shift in cancer therapeutics. Pembrolizumab, administered neoadjuvantly in cancers characterized by dMMR or MSI-H, has demonstrated both safety and remarkable outcomes.⁸⁰ The neoadjuvant intervention yielded high rates of pathologic, radiographic, and endoscopic response, thereby presenting significant considerations for the implementation of organ-sparing therapeutic approaches.⁸⁰

Beyond immunotherapy, neoadjuvant therapy with other tissue-agnostic agents have been explored in some pilot studies and this is an emerging area, given that patients are sequenced earlier at diagnosis. It offers several advantages such as those discussed earlier. For example, neoadjuvant dabrafenib/trametinib regimen has been used in patients with *BRAF* V600E-mutated anaplastic thyroid carcinoma and has demonstrated feasibility of complete resection, decreased need for tracheostomy, high pathologic response rates, and durable locoregional control with symptom amelioration.⁷⁸ Similarly, selpercatinib has been used as a neoadjuvant therapy in patients with advanced thyroid cancer with *RET* alterations.^{81,82} The use of larotrectinib has also been reported in the neoadjuvant setting of children with locally advanced *TRK* fusion positive sarcomas.⁸³ For children with locally advanced *TRK* fusion sarcomas, the prospect of surgical resection posttreatment with the selective *TRK* inhibitor, larotrectinib, emerges as an exciting option offering hope. This alternative avenue not only showcases promising outcomes but also offers a potential reprieve from the substantial morbidity associated with existing modalities. The findings from the neoadjuvant study with larotrectinib underscore the feasibility and efficacy of utilizing larotrectinib as a presurgical therapeutic intervention for children with newly diagnosed *TRK* fusion sarcomas. The implication of this approach goes beyond mere treatment; it signals a paradigm shift in the management of such pediatric malignancies (and adults), suggesting a path that holds promise for both clinical efficacy and a reduction in the adverse impacts of conventional treatments.

SUMMARY

The current approvals represent only the beginning of the era of tissue-agnostic precision therapies. The genomic revolution has led to an increased understanding of oncogenic alterations, cancer biology, and molecular pathways. It is increasingly evident that biomarkers are shared across multiple tumor types and are not restricted to one histology. Simultaneously, the exponential increase in the discovery of targeted therapies, immunotherapies, and antibody-drug conjugates to target these aberrant pathways across tumor types opens up options to expand therapeutic choices and expedite drug development. Tissue-agnostic drug development is also increasingly important for rare cancers that would otherwise not have access to alternative therapies. Early anecdotal and pilot studies have shown the potential benefit of neoadjuvant approaches with tissue-agnostic therapies. As more biomarkers are unraveled and more drugs are developed, the field is poised for further expansion. Finally, in diseases where drugs were generally ineffective or where surgical interventions had limited roles, it remains to be determined whether these new and highly active drugs will have roles in the neoadjuvant setting to convert unresectable to resectable disease

or in the adjuvant setting to decrease the risk of recurrence. Further trials are warranted to investigate these unanswered questions.

DISCLOSURE

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