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# Tumor-Agnostic Treatment for Cancer: When How is Better than Where

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**Abstract**

In the evolving landscape of precision oncology, genomic characterization of tumor has become crucial in order to move toward a molecular-based therapy for the vast majority of cancers. Recently, translational research has offered new perspectives in systemic cancer treatment thanks to the identification of novel oncogenic targets and the development of new targeted therapies, followed by the latest applications of genomic sequencing. Simultaneously, next-generation sequencing (NGS) has expanded its accessibility, being incorporated into clinical studies at the time of the initial screening, disease progression, and often in longitudinal monitoring of molecular changes. Consequently, new potentially targetable molecular alterations have been identified in several different types of tumors, leading to the development of tumor-agnostic treatments. Being highly selective for specific molecular alterations, these drugs are active against different subtypes of oncogene-addicted cancers. Three of these drugs—pembrolizumab [an anti-programmed death 1 (PD-1) monoclonal antibody (MAb)], larotrectinib [a pan-tropomyosin receptor tyrosine kinase (TRK) inhibitor], and entrectinib [a pan-TRK, anaplastic lymphoma kinase (ALK) and ROS-1 inhibitor]—received US FDA approval in 2017, 2018, and 2019, respectively. In this article, we critically review the clinical studies responsible for FDA approval and the most recently updated results. We then discuss the benefits and limitations of these new methodological approaches, paying particular attention to the largest precision medicine master protocol, NCI-MATCH. Among the benefits, there are the increased chances of offering targeted therapies for patients with specific alterations identified in different types of tumors. Among the limitations, we highlight that the same driver mutation may require different therapeutic strategies in different types of cancers. Additionally, the complex study design undeniably requires a dynamic strategy to enroll patients with considerable economic and managerial efforts.

## Key Points

Three drugs—pembrolizumab, larotrectinib, and entrectinib—received US FDA approval in 2017, 2018, and 2019, respectively.

New paradigms have been developed in clinical cancer research, in order to design clinical trials more suitable for treatment needs.

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## 1 Introduction

The evolving landscape of precision oncology requires a comprehensive knowledge of the molecular mechanisms underlying oncogenic pathway alterations. Genomic characterization of cancer has become crucial in order to offer highly effective treatments and avoid unnecessary adverse events to non-responders. Fortunately, in recent years, translational research has off ed new perspectives in systemic cancer treatment, first with the identification of novel oncogenic targets [e.g. REarranged during Transfection proto-oncogene (RET), tropomyosin receptor tyrosine kinase (TRK), fibroblast growth factor receptor (FGFR), etc.] and the development of new targeted therapies, and, second, by improving the methods and applications of genomic sequencing [1, 2].

Next-generation sequencing (NGS), with its short- and long-read applications, has expanded its accessibility as a result of the improved output promptness, the increasing availability of molecularly targeted drugs, and its cost-effective approach [3].

Simultaneously with these advances, clinical trials have become more dependent on tumor molecular profiling. As a result, these sequencing techniques have been incorporated into clinical studies, at the time of the initial screening, disease progression, and often in longitudinal monitoring of molecular changes [4–6].

New potentially targetable molecular alterations have been identified in several different types of tumors, leading to the development of so-called tumor-agnostic treatments [2, 6]. Being highly selective for specific molecular alterations, these drugs are active against diff ent subtypes of oncogene-addicted cancers [6].

On 23 May 2017, the US FDA approved pembrolizumab, a monoclonal antibody (MAb) that binds to the programmed death 1 (PD-1) receptor, as the fi t tumor-agnostic treatment. The indication included the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors that have progressed after prior standard treatment and who have no other satisfactory treatment option, or with MSI-H or dMMR colorectal cancer that has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [7].

Larotrectinib, the second tumor-agnostic drug, was approved by the FDA on 26 November 2018. Larotrectinib is indicated for adult and pediatric patients with unresectable or metastatic solid tumors harboring a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, and who have progressed after previous treatment or have no satisfactory standard treatment options [8].

On 15 August 2019, the FDA approved the third tumor-agnostic treatment, entrectinib, a potent multikinase pan-TRK inhibitor with additional activity against anaplastic lymphoma kinase (ALK), and ROS-1. The indication included the treatment of pediatric (≥12 years of age) and adult patients with solid tumors harboring NTRK gene fusion without a known acquired resistance mutation, metastatic disease, or where surgical resection is likely to result in severe morbidity, progression of disease after prior treatment, and/or no satisfactory standard treatment options. Entrectinib also received FDA approval for adult patients with metastatic NSCLC harboring ROS1 rearrangement [9]. The characteristics of these three drugs are shown in Table 1.

## 2 Neurotrophic Receptor Tyrosine Kinase (NTRK)

The TRK family includes TRKA, encoded by the gene NTRK1; TRKB, encoded by NTRK2; and TRKC, encoded by NTRK3. These receptors are involved in nervous system development and homeostasis, playing an important role in the regulation of neuronal differentiation and survival. The TRK receptors are also widely expressed in non-neural tissues, including lung, bone, pancreatic β-cell, and monocytes.

Three ligands specifically bind, with high affinity, at least one of the TRK family members: nerve growth factor (NGF) prevalently binds TRKA; brain-derived neurotrophic factor (BDNF) and neurotrophin 4 (NT-4) prevalently bind TRKB; and neurotrophin 3 (NT-3) prevalently binds TRKC. After ligand binding to one of the wild-type TRK family members, the activation of multiple intracellular signaling pathways occurs, including the MAPK, PI3K, and PKC pathways.

NTRK gene fusions, which are the most common events conferring oncogenic TRK activation, lead to the transcription of a chimeric oncoprotein. The product of the fusion is characterized by constitutive activation regardless of the presence of the specific ligands. Since 1982, when the first gene fusion was identified, more than 50 new fusion partners have been characterized, and they are heterogeneously associated with various types of cancer. These rearrangements are detected at frequencies higher than 90% in rare tumor types, such as secretory breast carcinoma, mammary analogous secretory carcinoma of salivary glands (MASC), and infantile fibrosarcomas, and frequencies of 70–85% in congenital mesoblastic nephroma [10, 11]. In contrast, they are detected at frequencies of 5–25% in other types of cancer, such as papillary thyroid cancer, Spitzoid neoplasms, pediatric gliomas, and wild-type gastrointestinal solid tumors (GISTs), and < 5% in other cancers, such as non-small cell lung cancer (NSCLC), cholangiocarcinoma, colorectal cancer, astrocytoma, melanoma, and head and neck cancer [10, 11].

Entrectinib and larotrectinib are currently FDA-approved for the treatment of cancer harboring NTRK gene fusions. Larotrectinib is a potent, highly selective inhibitor of all TRK members, with half maximal inhibitory concentration (IC$_{50}$) values of 5–11 nM. Using a large panel of non-TRK enzymes, larotrectinib also showed inhibitory activity against TNK2 at an approximately 100-fold higher concentration [8]. Entrectinib is active against all TRK members, ALK, and ROS-1, with IC$_{50}$ values of 0.1–2 nM, and also inhibits JAK2 and TNK2, with IC$_{50}$ values > 5 nM [9].

Three main trials evaluated the efficacy and safety of larotrectinib in NTRK fusion-positive patients with various tumor types. A phase I study enrolled adults (LOXO-TRK-14001, NCT02122913), a phase I–II study enrolled children (SCOUT, NCT02637687), and a phase II study enrolled adolescents and adults (NAVIGATE, NCT02576431) (Table 2). The fi t 55 patients enrolled across the three studies were included in a combined analysis with objective response rate (ORR) as the primary endpoint. Overall, 22% of patients had a salivary gland tumor, 20% had a soft tissue sarcoma, 13% had an infantile fi osarcoma, and 9% had a thyroid cancer. The analysis demonstrated the

**Table 1** First three tumor-agnostic treatments that received US FDA approval

| Drug | Molecular formula | Spectrum of activity | Date of US FDA approval | US FDA indication |
|---|---|---|---|---|
| Pembrolizumab [7] | $C_{6534}H_{10004}N_{1716}O_{2036}S_{46}$ | Anti-PD-1 MAb | 23 May 2017 | Pediatric and adult patients with unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed after prior standard treatment and who have no other satisfactory treatment options, or with MSI-H or dMMR colorectal cancer that has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan |
| Larotrectinib [8] | $C_{21}H_{22}F_2N_6O_2$ | Pan-TRK inhibitor | 26 November 2018 | Pediatric and adult patients with solid tumors that have NTRK gene fusion without a known acquired resistance mutation, metastatic disease, or where surgical resection is likely to result in severe morbidity, and have progressed after treatment or have no satisfactory standard treatment options |
| Entrectinib [9] | $C_{31}H_{34}F_2N_6O_2$ | Pan-TRK, ALK and ROS-1 inhibitor | 15 August 2019 | Pediatric ($\geq$12 years of age) and adult patients with solid tumors that have NTRK gene fusion without a known acquired resistance mutation, metastatic disease, or where surgical resection is likely to result in severe morbidity, and have progressed after treatment or have no satisfactory standard treatment options<br>Adults with metastatic NSCLC whose tumors are ROS-1-positive |

*dMMR* mismatch repair-deficient tumor, *MAb* monoclonal antibody, *MSI-H* high microsatellite instability, *NTRK* neurotrophic tyrosine receptor kinase, *PD-1* programmed death 1, *TRK* tropomyosin receptor tyrosine kinase, *ALK* anaplastic lymphoma kinase, *NSCLC* non-small cell lung cancer

remarkable activity of larotrectinib, regardless of tumor type or specifi TRK fusions, with an ORR of 75%, including 13% of patients who obtained a complete response (CR). Rapid and prolonged tumor responses were observed, with a median time to response of 1.8 months and a median duration of response not reached. Among all patients, the progression-free survival (PFS) rate at 12 months was 55%. Of note, radical surgery was performed in two patients with locally advanced infantile fibrosarcoma, since a tumor shrinkage under treatment occurred [8, 12]

Three multicenter, single-arm trials (ALKA-372–001, STARTRK-1, and STARTRK-2) explored the activity of entrectinib (Table 2) in patients with a wide range of unresectable or metastatic solid cancers harboring NTRK gene fusions. Data from the fi t 54 patients enrolled were collected to assess efficacy and safety. An ORR of 57.4% was reported, with CR in 7.4% of patients and a probability of no progression or death of 45% at 1 year [9, 13].

In more detail, ALKA-372-001 and STRTRK-1 were two phase I trials that enrolled a total of 119 patients, of whom 60 were rearranged in NTRK, ROS1, or ALK. Among the group of patients without rearrangements, 53 had point mutations, amplifications, copy number variants, or insertions/deletions, whereas 6 had no known alterations. Responses were only observed in patients harboring ALK,

ROS1, or NTRK rearrangements, with the exception of one patient with neuroblastoma harboring an ALK F1245V mutation. Of note, no responses were observed among patients with ROS1 or ALK rearrangement who were previously treated with crizotinib, ceritinib, or alectinib. In the analysis restricted to TKI-naïve patients treated with 600 mg daily, entrectinib showed activity on all three patients harboring an NTRK fusion, i.e. SQSTM1-NTRK1 in NSCLC, ETV6-NTRK3 in MASC, and LMNA-NTRK1 in colorectal cancer. Stable disease (SD) with remarkable clinical benefit was reported in one patient with a glioneuronal tumor harboring the BCAN-NTRK1 rearrangement. In these trials, responses were also observed in ROS1-rearranged NSCLC and ALK-rearranged NSCLC, renal cell carcinoma, and colorectal cancer. Entrectinib also showed encouraging activity in the central nervous system (CNS), both on metastatic lesions and primary brain tumors [14]. Moreover, in a phase I/Ib trial (STARTRK-NG), entrectinib demonstrated remarkable clinical activity in patients $\leq$20 years of age with refractory CNS or solid tumors harboring NTRK, ROS1, or ALK rearrangements [15].

The activity of entrectinib is currently being evaluated in a multicenter, phase II basket study (STARTRK-2 trial, NCT02568267), which is enrolling patients with NTRK, ROS1, or ALK fusion-positive cancers.

**Table 2** Summary of the main prospective trials that were crucial for US FDA approval of tumor-agnostic treatments

| Trial | Phase | Treatment | Study population | No. of patients | Primary endpoint | ORR (%) | PFS | OS |
|---|---|---|---|---|---|---|---|---|
| Combined analysis of LOXO-TRK-14001, SCOUT, and NAVI-GATE [8, 12] | I–II | Larotrectinib | Pediatric and adult patients with advanced NTRK fusion-positive tumor | 55 | ORR | 75 | 12-month PFS: 55% | NR |
| Pooled analysis of ALKA-372–001, STARTRK-1, and STARTRK-2 [9, 13] | I–II | Entrectinib | Unresectable or metastatic solid cancers of 10 tumor types harboring NTRK gene fusions | 54 | DLT, MTD, RP2D, ORR | 57.4 | 11.2 months | 20.9 months |
| Cohorts A and C from KEYNOTE-016 [21] | II | Pembrolizumab 200 mg q3w | Cohort A: dMMR metastatic colorectal cancer, after standard treatment failure<br>Cohort C: dMMR metastatic non-colorectal cancer, after standard treatment failure | 10<br>7 | Immune-related ORR and 20-week immune-related PFS rate<br>20-week immune-related PFS rate | 40<br>71 | 20-week immune-related PFS: 78%<br>20-week immune-related PFS: 67% | NR |
| Cohort A from KEY-NOTE-164 [23] | II | Pembrolizumab 200 mg q3w | MSI-H metastatic colorectal cancer, after at least two chemotherapy lines, including fluoropyrimidine, oxaliplatin, and irinotecan | 61 | ORR | 33 | 12-month PFS: 34% | 12-month OS: 72% |
| Selected patients from KEYNOTE-158 [24] | II | Pembrolizumab 200 mg q3w | MSI-H/dMMR cancers of 27 tumor types other than colorectal, after at least one prior regimen | 233 | ORR | 34.3 | 4.1 months | 23.5 months |

*dMMR* mismatch repair-deficient tumor, *MSI-H* high microsatellite instability, *NR* not reached, *NTRK* neurotrophic tyrosine receptor kinase, *OS* overall survival, *ORR* objective response rate, *PFS* progression-free survival, *q3w* every 3 weeks

## 3 Microsatellite Instability

MSI-H tumors are included in those harboring a dMMR system. These cancers are characterized by hypermutability of specific tandem DNA repeat sequences as a result of impaired DNA repair. The frequency of MSI-H signature is extremely variable across cancer types. Analyzing large cohorts of exomes and genomes across diff ent cancer types, the incidence of MSI-H was 16–19% among colon adenocarcinomas, 5–9% among rectal adenocarcinomas, 28–31% among uterine corpus endometrial carcinomas, 19–22% among gastric adenocarcinomas, 4–5% among adrenocortical carcinomas, and < 4% in other types of cancers. Overall, MSI-H tumors account for 3–4% of all cancers [16, 17]. These tumors most commonly arise from somatic mutations in sporadic cases; less commonly, they may be an expression of germline mutations within hereditary syndromes (e.g. Lynch syndrome).

There are several mechanisms responsible for the MSI-H phenotype, including mutation in the MLH1, MSH2, MSH3, MSH6, and PMS2 genes, hypermethylation of the MLH1 promoter and the epigenetic inactivation of MSH2, plus the downregulation of genes involved in mismatch repair systems by microRNAs [17, 18].

Harboring 10–100 times more mutations than mismatch repair-proficient (pMMR) tumors, dMMR tumors have been associated with high sensitivity to immunotherapy [19, 20]. The high concentration of tumor-infiltrating lymphocytes (TILs), specifically CD3+ and CD8+, within MSI-H tumors offers a possible explanation for the high immunogenicity [19]. The high mutational load, characteristic of dMMR tumors, has been thought to be responsible for high expression of neoantigens on the surface of tumor cells [19, 20]. In addition, high expression levels of PD-1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3) on TILs, and PD-ligand 1 (PD-L1) on tumor cells, have been found as a result of an immune-reactive microenvironment [19].

In the phase II KEYNOTE-016 trial (Table 2), 41 patients with stage IV disease were treated with pembrolizumab after standard treatment failure [21]. The study population included dMMR colorectal cancer (cohort A), pMMR colorectal cancer (cohort B), and dMMR endometrial, small bowel, gastric cancer or cholangiocarcinoma (cohort C). The evaluation of MMR status was carried out using the MSI Analysis System (Promega Corporation, Madison, WI, USA), with a specifi analysis of several tandem DNA repeat sequences involved in microsatellite instability. Among patients with dMMR tumors, 24 times more somatic mutations were observed on average compared with patients with pMMR tumors. In addition, in these patients, immunohistochemical analysis showed a higher density of CD8+ lymphoid cells and PD-L1 expression.

The primary endpoints for cohorts A and B were met, with an immune-related ORR of 40% in cohort A compared with 0% in cohort B, and 20-week immune-related PFS rates of 78% and 11%, respectively. Likewise, the primary endpoint for cohort C was met, with an immune-related PFS at 20 weeks of 67% and an ORR of 71%. Disease control rate (DCR) was 90% in cohort A and 71% in cohort C. Interestingly, all patients with dMMR tumors without Lynch syndrome had an objective response when compared with 27% of ORR in patients with Lynch syndrome. Median PFS and overall survival (OS) in cohort B were 2.2 and 5 months, respectively. In contrast, median PFS was 5.4 months in cohort C, and was not reached in cohort A. In addition, the median OS was not reached in both cohorts [21]. In an updated analysis of this study, ORRs were 52% and 54% in patients with MSI-H/dMMR colorectal cancer and other cancer types, respectively, with no signifi diff ence between patients with or without Lynch syndrome [22].

Similar results were obtained in cohort A of the phase II KEYNOTE-164 trial (Table 2). Among 61 previously treated colorectal cancer patients with MSI-H/dMMR, a remarkable activity of pembrolizumab was observed in all effi outcomes (ORR of 33%, 1-year PFS of 34%, and 1-year OS of 72%) [23].

In addition, data from another three multicohort trials (KEYNOTE-012, KEYNOTE-028, and KEYNOTE-158) (Table 2), including small groups of MSI-H/dMMR patients ($n = 6$, $n = 5$, and $n = 19$, respectively), were considered for FDA approval of pembrolizumab in patients with MSI-H/dMMR cancer [7].

More specifically, the multicohort KEYNOTE-158 trial evaluated the activity of pembrolizumab in patients with different types of cancer who progressed after prior standard treatments. An updated analysis of 223 patients with MSI-H/dMMR non-colorectal cancer from all cohorts, including cohort K, which was specifi for MSI-H/dMMR patients, showed an ORR of 34.3%, with a median time to response of 2.1 months. This trial confirmed the activity of pembrolizumab in these molecularly selected patients, with a median PFS of 4.1 months and estimated 2-year PFS and OS rates of 29.3% and 48.9%, respectively [24].

Consistent with these results, the phase II CheckMate142 trial showed a clear benefi off ed by the combination of nivolumab and ipilimumab in previously treated patients with MSI-H/dMMR colorectal cancer. In this cohort, ORR was 55% and DCR for at least 12 weeks was 80%, with 12-month PFS and OS rates of 71% and 85%, respectively. This study was crucial for FDA approval of ipilimumab in combination with nivolumab for the treatment of this molecularly selected patient population previously treated with a fluoropyrimidine, oxaliplatin, and irinotecan [25].

# 4 New Approaches in Drug Development

In the era of precision medicine, clinical research must be able to promptly transpose the advances in translational research, adjusting the usual designs of the clinical studies, in order to move toward a molecularly guided therapy for most cancers. In response to these changes, the need was felt to fi new paradigms in clinical cancer research that could be more suitable for treatment needs, fully exploiting the potential of tools for genome sequencing [1–5]. Master protocols have recently been developed for this purpose. The patient is initially screened to detect multiple potential molecular targets simultaneously. Once the driver mutation has been identified, the patient receives the specific targeted therapy within a clinical substudy. Thanks to this approach, the risk of screening failure is signifi y reduced and the patient's chances of receiving specifi treatment have increased. Consequently, the number of patients enrolled within clinical trials may increase and the scattering of patients within different studies with concurrent active enrolment may be reduced.

A basket trial is an example of a master protocol, involving diff ent types of cancer, in which patients with the same druggable molecular alteration are enrolled. In contrast, an umbrella trial enrolls patients with the same primary tumor class or location. After an initial screening in which molecular alterations are detected, patients are assigned to the appropriate subtrial to receive specific targeted therapies [5]. In this context, NCI-MATCH is a phase II study with an attractive design, and could be a model for generating further trials. In the first phase, patients are screened using NGS, after which approximately one-third of patients could probably be included in one of the 25 single-arm substudies (subsequently expanded to 35), in case a druggable mutation is detected. The primary endpoint is ORR [26]. In the last few years, preliminary results have been presented (Table 3). Among patients with dMMR endometrial, prostate, breast, and other types of cancer, nivolumab has shown moderate effi , with an ORR and DCR of 36% and 57%, respectively [27]. The selective FGFR inhibitor AZD4547 has demonstrated modest activity in patients with FGFR amplification, mutation, or fusion, with an ORR and DCR of 5% and 51%, respectively [28]. The pan-AKT inhibitor capivasertib demonstrated promising activity in patients diagnosed with tumors harboring AKT1 E17K mutation (ORR 23% and DCR 69%) [29]. Moderate clinical activity of ado-trastuzumab emtansine was observed in patients with human epidermal growth factor receptor 2 (HER2)-amplified cancers of different types, excluding breast and gastric cancers (ORR 5.6% and DCR 52.6%) [30]. In cohort I, the PI3K inhibitor taselisib showed a 6-month PFS rate of 27% in patients with activating mutations in PIK3CA, although no partial

response (PR) or CR were reported. Interestingly, the mutational co-occurrence rate was 67% [31]. Among patients with deleterious phosphatase and tensin homolog (PTEN) mutations or deletions, only 4.5% obtained a response with the PI3K β-selective inhibitor GSK2636771 [32]. Afatinib, an irreversible pan-HER inhibitor, showed disappointing activity in terms of ORR and 6-month PFS rates (2.7% and 11%, respectively) in HER2-mutated patients (excluding NSCLC), while a significant response was observed in one patient with adenocarcinoma of extramammary Paget's skin disease [33]. Among patients with CCND1–3-amplified cancers, a DCR of 38.9% and ORR of 0% were observed with the cyclin-dependent kinase 4 and 6 inhibitor palbociclib [34]. The Wee1 kinase inhibitor AZD1775 has shown modest clinical activity in heavily pretreated patients with BRCA1–2 mutations. Only 3.2% of patients had a clear response, with an overall 6-month PFS rate of 19% [35]. The combination of dabrafenib and trametinib has shown promising activity in patients with BRAF-V600E/K mutated cancers, excluding melanoma, colorectal, and thyroid cancer. In this cohort, ORR was 33.3% and the 6-month PFS rate was 70.6% [36].

Some other alterations (e.g. BRCA mutations, isocitrate dehydrogenase [IDH] mutations, and FGFR aberrations) may be predictive of the clinical benefi of specifi targeted therapies, and have been identifi as promising tumor-agnostic markers [37, 38]; however, tumor-agnostic markers must offer a similar therapeutic benefit on various types of cancer to be considered reliable. BRCA1/2 mutations are one the most studied biomarkers for tumor-agnostic treatment, as evidenced by the FDA approval of poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of breast, ovarian, pancreatic, and, in the future, prostate cancer. Although BRCA1/2 mutations have been detected in a wide range of cancer types, the extent of the clinical benefit provided by PARP inhibitors in patients with BRCA-mutant tumors differs according to tumor histology. In contrast, other biomarkers, such as the homologous recombination deficiency score, could better predict the efficacy of PARP inhibition in patients with BRCA-mutated cancers [37].

Several clinical trials are currently evaluating new targeted therapies for molecularly selected patients with various solid tumors. The phase II LODESTAR trial (NCT04171700) is studying the efficacy of rucaparib in patients with deleterious alterations in homologous recombination repair (HRR) genes. Cohort A is enrolling patients with mutations in BRCA1–2, PALB2, RAD51C, or RAD51D, whereas the exploratory cohort B is enrolling patients with mutations in BARD1, BRIP1, FANCA, NBN, RAD51, or RAD51B [40]. Another PARP inhibitor, IDX-1197, is currently under evaluation in the phase

**Table 3** Summary of the main preliminary results from the NCI-MATCH master protocol

| Reference | Treatment | Study population | No. of patients | ORR (%) | DCR (%) | Survival outcomes |
|---|---|---|---|---|---|---|
| Azad et al. [27] | Nivolumab (anti-PD-1) | dMMR non-colorectal cancers of various types (e.g. endometrioid endometrial adenocarcinoma, prostate adenocarcinoma, and uterine carcinosarcoma) | 42 | 36 | 57 | 18-month PFS rate: 31.4% Median OS: 17.3% |
| Chae et al. [28] | AZD4547 (FGFR inhibitor) | Tumors with FGFR amplification, mutation, or fusion (e.g. breast, urothelial, and endometrial) | 50 | 5 | 51 | 6-month PFS rate: 17% |
| Kalinsky et al. [29] | Capivasertib (pan-AKT inhibitor) | Tumors with AKT1 E17K mutation (e.g. breast, and endometrioid adenocarcinoma) | 35 | 23 | 69 | 6-month PFS rate: 52% |
| Jhaveri et al. [30] | Ado-trastuzumab emtansine (HER2-targeted antibody–drug conjugate) | HER2-amplified tumors, excluding breast and gastric cancers | 36 | 5.6 | 52.6 | 6-month PFS rate: 23.6% |
| Krop et al. [31] | Taselisib (PI3-kinase inhibitor) | Tumors with activating mutations in PIK3CA | 65 | 0 | NR | 6-month PFS rate: 27% |
| Janku et al. [32] | GSK2636771 (PI3K β-selective inhibitor) | Arm N: tumors with PTEN mutation/deletion Arm P: tumors with loss of PTEN | 22 / 34 | 4.5 / 0 | 36.5 / 37.5 | Median PFS: 1.8 months in both arms |
| Bedard et al. [33] | Afatinib (pan-HER inhibitor) | HER2-mutated patients, excluding NSCLC | 40 | 2.7 | NR | 6-month PFS rate: 11% |
| Clark et al. [34] | Palbociclib (cyclin-dependent kinase 4 and 6 inhibitor) | CCND1-3 amplified cancers | 40 | 0 | 38.9 | Median PFS: 1.8 months |
| Kummar et al. [35] | AZD1775 (Wee1 kinase inhibitor) | Tumors with mutations in BRCA 1–2 | 33 | 3.2 | NR | 6-month PFS rate: 19% |
| Salama et al. [36] | Dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) | Tumors with BRAF V600E/K mutations, excluding melanoma, and colorectal and thyroid cancer | 35 | 33.3 | NR | Median PFS: 9.4 months |

*DCR* disease control rate, *dMMR* mismatch repair-deficient tumor, *FGFR* fibroblast growth factor receptor, *HER2* human epidermal growth factor receptor 2, *NR* not reported, *NSCLS* non-small cell lung cancer, *OS* overall survival, *ORR* objective response rate, *PD-1* programmed death 1, *PFS* progression-free survival, *PTEN* phosphatase and tensin homolog

Ib/IIa VASTUS trial (NCT04174716), which is enrolling patients with HRR mutation [41]. In another ongoing trial (NCT03017521), patients with PI3K/AKT gene aberration are receiving a highly selective AKT inhibitor, TAS-117 [42]. The ongoing phase II trial CAPTURE (NCT03297606) has been designed to simultaneously evaluate 13 regimens (olaparib, dasatinib, nivolumab plus ipilimumab, axitinib, bosutinib, crizotinib, palbociclib, sunitinib, temsirolimus, erlotinib, trastuzumab plus pertuzumab, vemurafenib plus cobimetinib, vismodegib) for patients with solid cancers harboring druggable alterations such as VEGFR1–3, BCR-ABL, SRC, ALK, ROS-1, MET, POLE, POLD, BRCA1–2, FGFR1–3,

BRAF-V600, PTCH1, etc. [43]. The phase II FUZE trial (NCT03834220) is evaluating the efficacy of a pan-FGFR inhibitor debio 1347 in patients with FGFR1–3 gene rearrangements [44].

Although these new approaches have offered several advantages in the personalized treatment of cancer, they showed some limitations. First, the same driver mutation may require different therapeutic strategies in different types of cancer. The BRAF-V600E mutation, for example, occurring in approximately 50% of melanomas and 5–15% of colorectal cancers, has different rates of response to targeted therapies in these cancer types [51]. Excellent results have been obtained with BRAF inhibition and, better yet, with the combined BRAF

and MEK inhibition in melanoma [45, 46]. In contrast, mono-therapy with BRAF inhibitors has failed in colorectal cancer treatment [47]. The main mechanism responsible for the limited efficacy of BRAF inhibitors in colorectal cancer is the feedback activation of the EGFR pathway [48]. Triple combination strategies involving both BRAF and MEK inhibitors plus anti-EGFR MAbs or chemotherapy have been shown to improve the efficacy outcomes [49]. In addition, conducting precision medicine trials, such as basket, umbrella, or other master protocols, is challenging since researchers have to address several study problems and research questions simultaneously, and have to pay attention to the increased risk of false positive results. Being limited in sample size, the results of each single arm are obtained after a long period of time, with considerable economic and managerial efforts. Finally, the complex study design undeniably requires a dynamic strategy to enroll patients, and considerable flexibility to open and close subprotocol arms [52, 53].

## 5 Conclusions

In the last few years, the treatment strategy for the vast majority of cancers has become highly dependent on molecular profi   leading to the introduction of tumor-agnostic treatments (i.e. pembrolizumab, larotrectinib, and entrectinib). New trial designs have been developed to increase the chances of offering targeted therapies for patients with specific alterations identified in different types of tumors. Although promising, this approach needs to be further studied to definitively be considered practice changing.

### Compliance with Ethical Standards

**Conflict of interest**  Daniele Lavacchi, Giandomenico Roviello, and Alberto D'Angelo declare they have no conflicts of interest.

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