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REVIEW

Druggable targets meet oncogenic drivers: opportunities and limitations of target-based classification of tumors and the role of Molecular Tumor Boards

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The therapeutic landscape of cancer is changing rapidly due to the growing number of approved drugs capable of targeting specific genetic alterations. This aspect, together with the development of noninvasive methods for the assessment of somatic mutations in the peripheral blood of patients, generated a growing interest toward a new tumor-agnostic classification system based on 'predictive' biomarkers. The current review article discusses this emerging alternative approach to the classification of cancer and its implications for the selection of treatments. It is suggested that different types of cancers sharing the same molecular profiles could benefit from the same targeted drugs. Although recent clinical trials have demonstrated that this approach cannot be generalized, there are also specific examples that demonstrate the clinical utility of this alternative vision. In this rapidly evolving scenario, a multidisciplinary approach managed by institutional Molecular Tumor Boards is fundamental to interpret the biological and clinical relevance of genetic alterations and the complexity of their relationship with treatment response.

Key words: cancer, biomarker, target therapy, oncogenic drivers, Molecular Tumor Board

INTRODUCTION

The identification of therapeutic vulnerabilities based on deregulated signal transduction pathways has allowed the development of highly effective targeted drugs. There is much hope that predictive biomarkers will be used extensively and change traditional tumor classification criteria in a new system based on specific molecular aberrations (Figure 1). Such an approach may change the way by which oncologists will select systemic treatments.[1] The first example of this conceptual revolution regards pembrolizumab, an anti-programmed cell death protein 1 (PD-1) approved for metastatic or unresectable tumors with high microsatellite instability (MSI-H) or DNA mismatch repair deficiency. Furthermore, entrectinib has been approved to treat neurotrophic tropomyosin-receptor kinase (NTRK) fusion-positive cancers regardless of their location and histology.

'Druggable' are proteins involved in cell survival/proliferation, which may or may not be mutated but in any case must be deregulated, that can be targeted by specific drugs [i.e. epidermal growth factor receptor (EGFR) in lung cancer, vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) in renal cancer]. 'Actionable' is a more generic label given to those genetic aberrations involved in tumor cell growth which have an impact on clinical management of patients, a growing number of them being druggable and potentially responsive to targeted therapy.

Although treatment decisions are increasingly being guided by actionable mutations, several limitations in determining actionability need to be considered. For example, the genomic make-up of a tumor may vary due to tumor heterogeneity, the types of biopsy (i.e. primary or metastatic tumor sites, solid or liquid biopsies), and the time of biopsy sampling (before or after treatments). From the clinical pharmacology viewpoint, it may be conceivable

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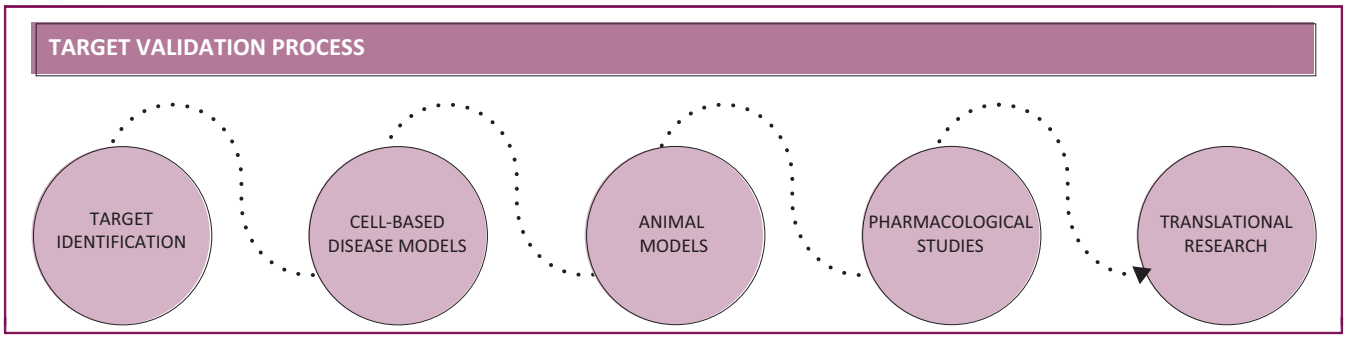

Figure 1. **The process of target validation including biomarker development.**

to classify genetic variants as *druggable* and *undruggable* depending on the availability of specific drugs.[2] Cancer pharmacology is moving toward a tumor-agnostic drug classification based on biomarkers that are both predictive and druggable, with important implications for the selection of treatments. Basket and umbrella clinical trials are now exploring alternative ways to accelerate drug development.

In this review article, we describe the biologic role of drug targets and their potential clinical relevance in the context of a personalized medicine approach, which is the working topic of Molecular Tumor Board (MTB).

ONCOGENES AND SIGNAL TRANSDUCTION PATHWAYS

EGFR/ErbB1

EGFR belongs to the c-erb superfamily of receptor tyrosine kinases (RTKs) that play a key role in cancer development and progression. Once bound to its ligands, EGFR can activate multiple signaling pathways, including RAS—RAF—MEK—ERK (extracellular signal-regulated kinase), phosphatidylinositol-3 kinase (PI3K), and protein kinase B (Akt).[3] The prevalence of *EGFR* mutations in non-small-cell lung cancer (NSCLC) is 32.3% (from 38.4% in Asian to 14.1% in Caucasian populations).[4] *EGFR* is altered in 6.82% of all cancers and the most common *EGFR* alterations are somatic mutation (7.26%) and amplification (2.83%).[5-8] Point mutations include L858R; the subclonal resistance mutations T790M and C797S are selected by previous treatments with EGFR tyrosine-kinase inhibitors (TKIs).[9] First-, second-, and third-generation drugs are gefitinib and erlotinib; afatinib; and rociletinib and osimertinib, respectively, the latter displaying high activity against T790M. The monoclonal antibodies (moAbs) cetuximab and panitumumab target ErbB1 and are used in colorectal cancer (CRC).[10]

NSCLCs harboring exon 19 deletion (ex19del) have higher overall response rate (ORR) and overall survival (OS) than those with exon 21 mutation (ex21mut).[11] Afatinib improves clinical outcomes in treatment-naïve patients with L858R or ex19del, compared with gefitinib, with a manageable tolerability profile.[12] Osimertinib has higher efficacy than first-generation EGFR TKIs with a similar safety profile.[13] Approximately half of patients treated with first- or second-generation drugs may acquire T790M-dependent drug resistance[14]; osimertinib[15] and rociletinib[16] are active in these patients. All EGFR mutations can be dynamically monitored using liquid biopsy (Table 1).

In conclusion, activating and resistance mutations are druggable and predictive of response to targeted drugs in NSCLC. No evidence has been reported in other cancer types (Table 1).

HER2/ErbB2

HER2/ErbB2 belongs to the ErbB family with complex involvement in cancer biology; this type of receptor, which does not have a specific ligand, transmits downstream signals by heterodimerization with other receptors in the family.[17] *HER2/ErbB2* is altered in 5.46% of all cancers with higher prevalence in breast cancer (BrCa), NSCLC, CRC, bladder, gastric, and gastroesophageal junction tumors. The most common alterations are amplification (3.82%) and mutation (3.69%), including S310F (0.32%), Y772_A775dup (0.28%), and L755S (0.23%).[5-8]

moAbs (pertuzumab, trastuzumab), antibody—drug conjugates (trastuzumab-emtansine, trastuzumab deruxtecan), and TKIs (lapatinib, neratinib and tucatinib) are HER2/ErbB2-targeting agents and are standard of care in HER2+ cancers.[18-20] (Table 1). *HER2* aberrations may develop in NSCLC after first- or second-generation EGFR TKIs[14,21] and also as a primary event.[21] Although limited by the small sample size, clinical trials demonstrated that NSCLC[22,23] and CRC[24] are also sensitive to HER2 targeting by moAbs, antibody—drug conjugates, or TKIs.

HER2 can be therefore classified as druggable, due to strong clinical evidence showing a relationship between HER2 positivity and clinical outcomes in BrCa, gastric, and gastroesophageal junction cancer patients (Table 1).

c-Met

The mesenchymal—epithelial transition factor (c-Met) is a RTK stimulated by the hepatocyte growth factor (HGF). In cancer cells, aberrant activation of the HGF—c-Met axis due to *c-Met* gene mutations, overexpression, or amplification can activate several signaling pathways, including PI3K/AKT and RAS/ERK. *c-Met* alterations occur in 2.71% of cancers including NSCLC, melanoma, CRC, malignant glioma, and BrCa. Mutations (2.53%) include amplification (0.71%), X1010_splice (0.13%), and X963_splice (0.08%).[5-8]

Table 1. Biomarkers and available drugs

Name of marker	Druggable/actionable alterations	Tumor type	Predictive value, LoE (e.g. available drugs)	FDA-approved liquid biopsy CDx test
EGFR/ErbB1	Mutations (e.g. L858R, ex19del, T790M)	NSCLC	1 (gefitinib, erlotinib, afatinib, osimertinib, dacomitinib)	Yes
HER2/ErbB2	Amplification	Breast	1 (trastuzumab, T-DM1, trastuzumab + pertuzumab, lapatinib, neratinib)	No
	Amplification	Esophagogastric	1 (trastuzumab)	No
	Point mutations (V659E)	NSCLC	3A (lapatinib)	No
c-Met	ex14 skipping mutations, amplification	NSCLC	1 (crizotinib, capmatinib, savolitinib*, tepotinib)	No
RET	Fusion	NSCLC	1 (selpercatinib, pralsetinib), 2A (cabozantinib), 3A (vandetanib)	No
ALK	Fusion	NSCLC	1 (crizotinib, alectinib, ceritinib, lorlatinib), 3A (brigatinib)	Yes (alectinib)
	Mutations (L1196M, L1196Q)	Soft tissue sarcoma	2A (crizotinib, ceritinib)	No
ROS1	Fusion, mutation	NSCLC	1 (crizotinib, entrectinib)	No
NTRK	Fusion	All tumors	1 (larotrectinib, entrectinib)	No
c-Kit	Mutations (e.g. 449_514mut), deletions (e.g. D419del)	GIST	1 (imatinib, sunitinib, regorafenib), 2A (sorafenib)	No
		Thymic tumors	2A (sunitinib)	No
	Mutations (e.g. K642E)	Melanoma	2A (imatinib)	No
PDGFR	Mutations (e.g. D842V), deletions (e.g. C456_N468del)	GIST	2A (imatinib, dasatinib)	No
		Leukemia, myelodysplasia	1 (imatinib)	No
FGFR1	Amplification	LSCC	3A (erdafitinib)	No
		NSCLC	3A (AZD4547)	No
FGFR2	Fusion, mutation	Bladder, cholangiocarcinoma	1 (erdafitinib, pemigatinib)	No
	Amplification	Breast	3A (dovitinib)	No
FGFR3	Fusion, mutation	Bladder	1 (erdafitinib)	No
RAS	Wild-type	CRC	1 (cetuximab, panitumumab)	No
BRAF	Mutations (e.g. V600E)	Melanoma	1 (vemurafenib, dabrafenib, trametinib, combo), 3A (trametinib)	No
		NSCLC	1 (dabrafenib + trametinib)	No
		Histiocytosis	3A (cobimetinib)	No
	Mutation (V600E)	CRC	1 (encorafenib + cetuximab)	Yes
	Fusions	Ovarian	3A (trametinib, cobimetinib)	No
MEK	Mutations	Melanoma, NSCLC, ovarian, histiocytic disorder	3A (trametinib, cobimetinib, selumetinib)	No
mTOR	Mutations (e.g. E2014K)	Bladder, RCC	3A (everolimus, temsirolimus)	No
AKT	Mutation (E17K)	Breast, ovarian	3A (capivasertib)	No
PTEN	Homozygous deletions, loss-of-function mutations	Breast	2A (capivasertib)	No
PIK3CA	Mutations	Breast	1 (alpelisib)	Yes
CDK4	Amplification	Soft tissue sarcoma	2A (palbociclib)	No
IDH1	Mutations	AML, cholangiocarcinoma	1-3A (ivosidenib)	No
IDH2	Mutations	AML	1 (enasidenib)	No
BRCA1/2 and ATM	Mutations (somatic)	Breast	1 (olaparib, talazoparib, rucaparib)	No
	Mutations (somatic)	Ovarian, prostate	1 (rucaparib, olaparib)	Yes
ERα	Mutations (e.g. E380Q)	Breast	2A (fulvestrant)	No
MSI-H	Not applicable	All	1 (pembrolizumab)	Yes
TML	Not applicable	Multiple tumor types	1 (pembrolizumab, nivolumab)	No

AML, acute myeloid leukemia; CRC, colorectal cancer; GIST, gastrointestinal stromal tumors; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; NSCLC, non-small-cell lung cancer; LSCC, lung squamous cell carcinoma; RCC, renal cell carcinoma; CDx, Companion Diagnostics; *, MET and EGFR.
LoE, level of evidence was based on the AACR Project GENIE database[8] and the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT).[138]
Classification criteria include tumors having alterations for which FDA-approved drug or standard care is available (1 or 2A), that are Level 1 or 2A in other tumor types (2B), and for which clinical evidence for response to investigational therapies in the same disease does exist (3A).

HGF—c-Met can be targeted by TKIs including (i) selective type I inhibitors (e.g. crizotinib, savolitinib, tepotinib) that competitively bind to the active c-Met conformation; (ii) nonselective type II inhibitors (e.g. cabozantinib, foretinib) that bind to the c-Met inactive conformation; and (iii) nonselective type III inhibitors (e.g. tivantinib) that do not compete with ATP binding. moAbs can be directed against c-Met (e.g. emibetuzumab, onartuzumab) or HGF (e.g. ficlatuzumab, rilotumumab).[25]

c-Met alterations in cancer are associated with shorter survival and response to targeted drugs; in renal cell carcinoma (RCC), NSCLC, and CRC the predictive value of *c-Met*+ versus *c-Met*− was demonstrated.[25-28]

Druggable aberrations with the highest predictive power are exon 14 skipping (ex14skip) mutations[29]; crizotinib, capmatinib, and tepotinib received a breakthrough Food and Drug Administration (FDA) approval in NSCLC patients harboring ex14skip due to the improvement in OS.[30,31]

In conclusion, *c-Met* aberrations can be classified as druggable with high predictive value in NSCLC (Table 1).

RET

The *RET* proto-oncogene encodes an RTK that binds ligands belonging to the glial cell-derived neurotrophic factor family, including glial cell-derived neurotrophic factor, neurturin, artemin, and persephin. *RET* is altered in 2.53% of cancers including NSCLC, CRC, BrCa, melanoma, and thyroid tumors. Mutations (2.78%) and gene loss (0.18%) are commonly observed in *RET*+ patients; relevant genetic alterations are M918T (0.13%), D567N (0.03%), and amplifications (0.08%).[5-8] Gain-of-function mutations of *RET* cause sporadic and familial medullary thyroid carcinoma, and multiple endocrine neoplasia 2A syndrome, whereas loss-of-function aberrations occur in Hirschsprung's disease. *RET* is activated by fusion to form the chimeric oncogene *RET*/papillary thyroid carcinoma.[32] Multikinase inhibitors are cabozantinib and vandetanib, whereas selective drugs include selpercatinib and pralsetinib.[33,34] RET inhibitors are active in several tumors, including NSCLC.[35]

Actionability of RET alterations is demonstrated in several cancers.[36] NSCLC patients with *RET* rearrangements (e.g. *KIF5B—RET* fusion) respond to cabozantinib[37] and vandetanib.[38] Patients with *RET*-mutant NSCLC and medullary thyroid carcinoma treated with pralsetinib experienced durable clinical responses with manageable toxicity profiles.[39] Furthermore, case report studies showed clinical response after treatment with cabozantinib in a metastatic BrCa patient with the *NCOA4—RET* fusion progressing to HER2-targeted therapy[40] and in a late-stage NSCLC patient with the *KIF5B—RET* gene fusion.[41] Finally, osimertinib combined with pralsetinib induces response in double *EGFR/RET*-mutant NSCLC patients.[42]

In conclusion, *RET* aberrations are druggable and further investigation using well-designed clinical trials with sufficient statistical power is needed to confirm the possible histology-independent classification of RET-driven tumors.

ALK/ROS1

The anaplastic lymphoma kinase (ALK) is a RTK involved in several tumors, including NSCLC and anaplastic large cell lymphomas. ALK recognizes some different ligands, including pleiotrophin and neurite growth-promoting factor 2 (NEGF2).[43] Alterations including *ALK* fusion, *ALK* copy-number gain, and activating *ALK* mutations are found in multiple cancers.[44] *ROS1* gene encodes a receptor that belongs to the ALK/leukocyte TK (LTK) and insulin RTK families and, once activated, induces cell proliferation by stimulating MAPK (mitogen-activated protein kinase)/ERK, PI3K/AKT, and JAK/STAT3 (Janus kinase/signal transducers and activators of transcription 3) signaling pathways. The homology to ALK accounts for the development of drugs targeting both.[45] *ALK* is altered in 3.21% of all cancers with NSCLC, CRC, melanoma, BrCa, and uterine corpus neoplasm having the greatest prevalence, the most common aberrations being fusion (∼5%), mutation (3.81%), missense mutations (3.48%), amplification (0.12%), and point mutations F1174L (0.03%) and P367R (0.03%).[5-8]

First-, second-, and third-generation ALK/ROS1 inhibitors such as crizotinib, alectinib, ceritinib, brigatinib, lorlatinib, can be used depending on the resistance mutation on which they are active, including L1196M, D1203N, F1174L, G1202R, C1156Y, and G1269A.[46,47]

Crizotinib is superior to chemotherapy in previously treated, advanced *ALK*- or *ROS1*-rearranged NSCLC patients.[48-50] Ceritinib,[51,52] alectinib,[53,54] and brigatinib[55] are superior to crizotinib in untreated *ALK*+ NSCLC. Lorlatinib, a third-generation inhibitor, may represent an effective treatment option in first-line or subsequent lines of therapy due to the central nervous system activity in *ALK*+ and *ROS1*+ patients.[56-59] The *ALK*+ inflammatory myofibroblastic tumor treated with crizotinib displayed a higher percentage of objective responses than *ALK*—.[60] An optimized sequence of ALK inhibitors may increase survival in patients.[61]

In conclusion, a large amount of clinical evidence demonstrates that target-based stratification is an optimal strategy to select patients who will benefit from ALK inhibitors (Table 1). The same approach for other cancer types requires further investigation.

NTRK

NTRK1-3 activate PI3K, RAS/MEK/ERK, and phospholipase C (PLC)-γ pathways during neuronal development and are extremely rare drivers of a variety of cancers, with *NTRK3* fusions being more common in secretory BrCa, mammary analog secretory carcinoma, and congenital fibrosarcomas. The most common *NTRK1* alterations are mutation (2.09%) and amplification (0.43%); among mutations, R214W (0.03%), R157H (0.02%), and T434M (0.02%) are the most frequent.[5-8] The most common alterations of *NTRK2* are mutation (1.39%), mainly A662T (0.02%) and V606I (0.02%); amplification (0.04%); and loss of function (0.03%).[5-8] Finally, *NTRK3* genetic abnormalities are mutation (2.61%), amplification (0.10%), and loss (0.04%); relevant *NTRK3* mutations are K746T (0.02%) and R306H (0.02%).[5-8] Potent and selective NTRK inhibitors are entrectinib and larotrectinib; nonselective inhibitors are also available.[62] Entrectinib induces durable responses in adult or pediatric patients with advanced NTRK fusion-positive solid cancers regardless of the tumor type,[63] and the same evidence was provided for larotrectinib.[64,65] FDA has approved NTRK TKIs for tumor-agnostic indication due to its recognized clinical efficacy in multiple cancer types.[66]

NTRK TKIs have proven clinical efficacy in *NTRK* fusion-positive cancers. The availability of validated methods for NTRK analysis makes this biomarker a successful example of the application of target-based classification of tumors (Table 1).

c-Kit

The proto-oncogene *c-Kit* encodes for a RTK belonging to the PDGF/c-Kit family that can bind stem cell factor; mutant

c-Kit has been implicated in the tumorigenesis of melanoma, acute myeloid leukemia (AML), and gastrointestinal stromal tumors (GISTs).[67] *c-Kit* is altered in 2.99% of cancers with connective and soft tissue neoplasms, NSCLC, melanoma, glioma, and CRC having the highest prevalence. The most common alterations are mutations (3.38%), amplifications (0.64%), and deletions (0.54%); clinically relevant missense mutation is D816H (0.12%).[5-8] In GIST, *c-Kit* mutations occur more frequently in exon 11 (70%), and exons 9, 13, 14, and 17.[68] c-Kit multitargeted TKIs include imatinib, dasatinib, and nilotinib, which also inhibit platelet-derived growth factor receptor (PDGFR)-α, PDGFR-β, and ephrin RTKs.[69] Adjuvant imatinib has been associated with reduced recurrence rates and improved OS in high-risk primary GIST,[70] whereas dasatinib induces high response rates in TKI-naïve GIST.[71]

c-Kit overexpression is a strong negative prognostic factor in NSCLC[72]; imatinib has no activity in *c-Kit* overexpressing small-cell lung cancer (SCLC) owing to the lack of *c-Kit* activating mutations.[67]

Imatinib is effective in *c-Kit*-mutated melanoma, a rare clinicopathological entity mainly located at acral and mucosal sites,[73] but not in *c-Kit*-amplified tumors.[74] Nilotinib is active in imatinib-treated patients,[75] while dasatinib response rate is low among *c-Kit*+ melanoma.[76] Sunitinib shows activity in the treatment of mucosal and acral melanoma, regardless of the presence of a c-Kit mutation.[77] c-Kit is mutated in 60%-80% of AML patients[78] and inhibitors may play a therapeutic role.[79]

In conclusion, *c-Kit* activating mutations appear to be druggable and predictive of response (Table 1). Further clinical investigations are needed to clearly establish the reliability of a target-based tumor classification.

PDGFRα

The platelet-derived growth factor receptor alpha (*PDGFRα*) gene is mutated in GIST (5%-10%), NSCLC (6%), CRC (5%), and gliomas (1%); gene amplifications and fusions are observed in glioblastoma (12%),[5-8,80] hypereosinophilic syndrome,[81] and dermatofibrosarcoma protuberans.[82] Multitargeting TKIs with PDGFRα-inhibitory activity include imatinib, sunitinib, regorafenib, crenolanib, and avapritinib.[83]

Activating mutations of *PDGFRα* are uncommon in GISTs (5%-10%) and mutually exclusive with *c-Kit* but confer sensitivity to imatinib.[84,85] *PDGFRα* D842V mutation is associated with resistance to imatinib, sunitinib, and regorafenib,[84] but sensitive to crenolanib and avapritinib,[84] while Y288C is a resistance mutation to PDGFR inhibitors.[80]

In conclusion, GISTs must be analyzed for mutations in *c-Kit* and *PDGFRα* at the time of diagnosis to guide treatment strategies based on targeted drugs (Table 1).

FGFR

Fibroblast growth factors (FGFs) and their receptors (FGFR1-4) have a pathogenic role in cancer.[86] *FGFR2* fusions or rearrangements occur in 10%-16% of intrahepatic cholangiocarcinomas[87] while *FGFR3* is altered in 4.81% of all cancers including bladder, BrCa, lung, ovarian, stomach, gliomas, and sarcomas.[88] The most common alterations in *FGFR3* are amplifications (2.53%) and mutations (0.36%), including R181H (0.01%) and E189K (0.01%).[5-8] Pan-FGFR inhibitors include erdafitinib and rogaratinib,[89] while infigratinib and pemigatinib are two selective and potent inhibitors of FGFR1-3.[90] Patients harboring FGFR2 fusions or rearrangements had a 35.5% objective response to pemigatinib.[91] Previously treated patients with locally advanced and unresectable or metastatic urothelial carcinoma harboring *FGFR* alterations respond favorably to erdafitinib.[92]

In conclusion, *FGFR2/3* alterations may predict response to selective FGFR inhibitors in multiple cancers (Table 1). In line with this notion, phase II and III trials are ongoing to test safety and efficacy of pemigatinib for various FGFR-driven tumors.

VEGF/VEGFR

The VEGF and its receptor (VEGFR) play a major role in cancer by regulating angiogenesis (VEGF-A and VEGFR-1/2) and lymphangiogenesis (VEGF-C/D and VEGFR-3). Angiopoietin and its receptors (TIE1-2) are also involved in pathological neovascularization.[93] The VEGF—VEGFR axis is targeted by moAbs (e.g. bevacizumab, ramucirumab), and VEGFR TKIs (e.g. sorafenib, sunitinib, axitinib, tivozanib, pazopanib, regorafenib, and cediranib).

Anti-VEGF/VEGFR agents are successfully used in multiple cancer types including RCC, CRC, hepatocellular carcinoma, NSCLC, and cervical cancer. For others (e.g. glioblastoma, BrCa, and ovarian cancers), the increase in progression-free survival (PFS) was not associated with OS improvement.[94] Anti-angiogenic drugs are used for diverse purposes, for example, chemo-potentiation in NSCLC, maintenance in ovarian cancer, and immune system regulation in combination with checkpoint inhibitors.[7,8,94] Unfortunately, predictive biomarkers of response are lacking.[95] However, a recent study showed that a composite model using VHL, TP53, and VEGFR-1 predicted PFS on first-line VEGF-targeted therapies in RCC.[96]

In conclusion, no single actionable mutations were found in VEGF/VEGFR (Table 1); however, the investigation of predictive biomarkers should be encouraged in prospective clinical trials to optimize VEGF-targeted therapies.

RAS

RAS mutations are frequent in several cancers[8,97,98]; in particular, *KRAS* (overall, 14%) is mutated in pancreatic cancer, NSCLC, and CRC; *NRAS* (2.6%) in melanoma and AML; and *HRAS* (1%) in bladder cancer.[8,99] The most common alterations in *KRAS* are mutations (20.6%), among which codon 12 missense (15.9%)—particularly G12D (5.6%)—is the most common.[5-8] *KRAS* or *NRAS* mutations in exons 2-4 are found in 50% of CRC patients; they are predictive of resistance to anti-EGFR treatments, thus limiting the use of panitumumab and cetuximab to

patients with RAS wild-type tumors and chemotherapy/antiangiogenic drugs to *RAS*-mutated cancers.[10,100] Several covalent *KRAS* G12C inhibitors, such as sotorasib (AMG-510), adagrasib (MRTX849), and JNJ-74699157, are in clinical development.[101-103]

In conclusion, *RAS* mutations are difficult to target because GTP binds the guanosine triphosphate/guanosine diphosphate pocket—the only one that can be targeted by small molecules—with extremely high affinity[103]; however, the new drugs give hope that KRAS will eventually become a druggable target.

BRAF

BRAF is altered in 7%-15% of all cancers including CRC, melanoma, NSCLC, papillary thyroid carcinoma, hairy cell leukemia (HCL), Langerhans cell histiocytosis, and Erdheim—Chester disease.[8,104] The most common alterations in *BRAF* are mutations and amplifications and are mutually exclusive with *RAS* aberrations.[5-8] The glutamic acid substitution within the activation segment of the kinase domain, resulting from V600E missense mutation, constitutively activates the MEK—ERK pathway. Atypical, non-V600 *BRAF* mutants are found in NSCLC but are rare in CRC.[105] Approximately 50% of melanomas harbor activating *BRAF* V600 mutations with the V600E variant accounting for up to 90% of cases.[106]

Selective BRAF TKIs include vemurafenib, encorafenib, and trametinib; a high response rate is obtained with vemurafenib in *BRAF* V600E/K-mutated melanomas,[107] which is further increased by combination with MEK inhibitors (i.e. dabrafenib/trametinib).[108-111]

BRAF mutations occur in 10% of CRC and are fourfold higher in patients with right- than left-sided cancer.[112] Combination of encorafenib and the MEK inhibitor binimetinib plus cetuximab to suppress EGFR-mediated resistance improves OS in this poor-prognosis population.[113]

Vemurafenib is effective in relapsed/refractory *BRAF*-mutated HCL with an ORR of 91% at 1 year.[114] Resistance frequently occurs and the BRAF/MEK TKI combination is not more effective over BRAF TKI alone[114]; however, relapsed/refractory HCL patients may well respond to vemurafenib/rituximab.[115] *BRAF* mutations are found in 1-2% of NSCLC and dabrafenib showed 33% ORR in pretreated patients[116]; the BRAF/MEK TKI combination shows encouraging activity in first line setting.[117]

In conclusion, *BRAF* V600 mutations are druggable in some, but not all, cancers (Table 1). This statement is in line with data obtained in V600 mutation-positive nonmelanoma patients treated with vemurafenib.[118]

MEK

MEK (also known as MAPK) serves as a downstream target for both RAS and BRAF proteins. *MAPK1* is altered in 0.75% of cancers including NSCLC, bladder, CRC, BrCa, and endometrium.[8] The most common alterations are mutations (0.51%, 0.07% of which are E322K), amplifications (0.26%), A7 duplication (0.12%), and gene loss (0.07%).[5-8]

Binimetinib, trametinib, and cobimetinib are MEK inhibitors; their combinations with BRAF TKIs significantly improved OS in *BRAF* V600E/K melanoma patients, as compared with single agents.[108,119,120]

In conclusion, MEK inhibitors are currently used in combination and the clinical perspectives of these drugs are in BRAF—RAS—ERK-driven tumors.

PI3K/AKT/mTOR

The PI3K/AKT/mTOR pathway plays a pivotal role in cancer and is negatively counterbalanced by phosphatase and tensin homolog (PTEN).[121,122] However, PTEN activity is frequently lost, leading to constitutive PI3K/AKT/mTOR activation, a poor prognosis indicator.[122,123] Mutations occur in the p110α catalytic subunit of *PI3K* (PIK3CA) and are detectable in gastric cancers (18%), CRC (15%), BrCa (20%-50%), and head and neck squamous cell cancers (HNSCCs; 30.5%), whereas genomic amplification is more frequent in NSCLC.[122] Loss of *PTEN* is observed in CRC (20%-40%), whereas mTOR activation occurs in bladder and prostate cancers (∼40%); BrCa and ovarian cancers (∼40%) and prostate cancers (∼50%) show increased AKT1 activity.[123]

Abnormalities of the *PIK3CA* gene copy number and missense mutations result in persistent activation of PI3K. Most common point mutations are H1047R (4.3%), E545K (3.7%), and E542K (2.3%).[7,8,124] *AKT1* displays mutation [2.09%, including E17K (1.26%)], amplification (0.30%), and gene loss (0.07%)[8] in human cancers, with actionable mutations being uncommon.[124-127] Activation of the PI3K/AKT pathway plays a role in Burkitt lymphomagenesis and is associated with worse outcomes.[128,129] Finally, *mTOR* aberrations are rare; the most frequent are E1799K (0.05%) and gene amplification (0.04%).[8]

Pathway inhibition can be achieved by targeting mTOR (temsirolimus and everolimus), PI3K (alpelisib and taselisib), and AKT (ipatasertib, capivasertib).[130]

PIK3CA and/or *PTEN* aberrations predict response to PI3K/AKT/mTOR inhibitors in a histology-independent fashion.[130] *PIK3CA* hotspot mutations may predict response to taselisib in patients with advanced solid tumors.[131] Taselisib plus fulvestrant induced a higher ORR in patients with *PIK3CA*-mutated versus nonmutated BrCa.[132] Alpelisib is active in *PIK3CA*-mutated solid tumors,[133] and in combination with fulvestrant prolongs PFS in previously treated *PIK3CA*-mutated BrCa,[134] although tumors with *PIK3CA* mutations occasionally do not respond to these drugs.[135] PI3K/AKT inhibitors are used in refractory, indolent, and aggressive B-NHLs.[136,137] *PIK3CA* aberrations are classified as tier IA (high level of evidence), according to the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT).[138]

In conclusion, the PI3K/AKT/mTOR pathway may offer both actionable (PTEN aberrations) and druggable (PIK3CA

mutations) targets (Table 1). It is worth noting that *PIK3CA* and *KRAS* mutations may co-occur, suggesting that a more comprehensive screening is advisable.

CDK4/6

The cyclin D/cyclin-dependent kinase 4/6 (CDK4/6) is a molecular complex that plays a pivotal role in cell cycle progression from the G1 to S phase due to phosphorylation of Rb1 and loss of repression of the E2F transcription factor. Several types of cancers display activation of the cyclin D/CDK4/6 pathway; cyclin D1 (*CCND1*) gene amplification was reported in ∼15-20% of human BrCa.

Palbociclib, ribociclib, and abemaciclib are third-generation inhibitors of CDK4/6 and *Rb1* aberrations are a promising biomarker so far.[139]

Actionable mutations or deregulated expression of *PIK3CA*, *AKT*, *mTOR*, *VEGFR1/2/3*, *PDGFRβ*, *c-Kit*, *FGFR1/2/3/4*, *MEK*, *JAK1/2*, *STAT3/5*, and *CDK2/7/9* is involved in resistance to CDK4/6 inhibitors[7,140]; *CDKN2A/2B* loss could predict sensitivity to CDK4/6 inhibition.[141]

In conclusion, although preclinical studies identified some potential actionable alterations, no clinical evidence has been provided so far that these alterations can predict response to CDK4/6 inhibitors in patients with multiple cancer types (Table 1). Nonetheless, this drug class is commonly used in combination with endocrine therapy in BrCa patients.

IDH1/2

Mutant isocitrate dehydrogenases 1 and 2 (*IDH1/2*) produce 2-hydroxyglutarate, and are involved in chromatin remodeling. *IDH1* is altered in ∼3% of cancers with glioblastoma, oligodendroglioma, astrocytoma, AML, and bile duct carcinoma having the greatest prevalence.[8,142] The most common *IDH1* alterations are mutations (4%), including missense R132H/C/L (2%, 0.8%, and 0.14%, respectively).[5-8] *IDH2* is altered in 1.13% of cancers including AML, BrCa, CRC, NSCLC, and myelodysplastic syndromes; commonly observed alterations are mutation (1.35%), missense mutations in codons 140 (0.41%, R140Q 0.38%) and 172 (0.34%), and amplification (0.2%).[8]

Owing to their role in leukemogenesis,[143,144] inhibitors of IDH1/2 (ivosidenib, enasidenib) were developed for the treatment of AML.[145]

Ivosidenib induces durable remission in *IDH1*-mutant AML,[146] while enasidenib is active in AML harboring *IDH2* mutations in codons 140 and 172[147,148]; however, resistance may develop due to second-site Q316E and I319M mutations.[149] It is unclear whether IDH inhibitors are effective therapeutic strategy in glioma, as their ability to cross the blood—brain barrier remains unclear.[150] The IDH1/2 inhibitor vorasidenib crosses the blood—brain barrier and is being developed for the treatment of low-grade IDH-mutant glioma.[151] Another element of uncertainty is the prognosis of gliomas which seems to be better in mutated cases.[152]

In conclusion, clinical evidence indicates that *IDH* mutations can be considered druggable targets in AML but not in glioma (Table 1).

NUCLEAR PROTEINS

PARP

Poly (ADP-ribose) polymerases (PARPs) have a key role in DNA repair; PARP inhibition increases tumor sensitivity to DNA-damaging agents by destabilizing replication forks and inducing death in cells lacking proficient homologous recombination mechanisms (e.g. *BRCA1* and *BRCA2* mutants).[153] *BRCA1* is dysfunctional in 3% of cancers including NSCLC, BrCa, CRC, ovarian, and melanoma, with the most common alterations being mutations [both germline and somatic (3%)] and frameshifts (0.4%).[8,54] Germline *BRCA* mutations were reported in 4-7% of patients with pancreatic cancer.[154] *BRCA2* is altered in 4.6% of cancers including CRC, NSCLC, BrCa, prostate, and bladder; the most common alterations are mutations (5.23%) and frameshifts (0.94%).[8]

PARP inhibitors (olaparib, niraparib, rucaparib, and talazoparib) have high efficacy against *BRCA*-mutated tumors, particularly ovarian cancer.[155,156] In this disease, veliparib significantly improves PFS in BRCA mutants after induction therapy,[157] while olaparib provides a significant PFS gain in homologous recombination-deficient tumors.[158] Niraparib increases PFS in patients previously treated with platinum-based schedules, regardless of BRCA mutations.[159] The same clinical benefit was observed with talazoparib in *BRCA1/2*+ BrCa patients[160] and with olaparib in metastatic pancreatic cancer.[161] Rucaparib is effective in advanced ovarian cancer with deleterious germline and/or somatic *BRCA* mutations.[162]

In conclusion, *BRCA* mutations in ovarian and BrCa patients are actionable targets that predict response to PARP inhibitors. The strength of evidence is lower for somatic than germline *BRCA* mutations (Table 1). For other types of cancer (e.g. prostate, pancreatic, and SCLC), the predictive role of *BRCA* status on the response to PARP inhibitors must be consolidated.

ERα and ERβ

Estrogen receptors (ERα and ERβ) belong to the steroid/nuclear receptor superfamily and play a pivotal role in endocrine regulation of BrCa.[163,164] ERα is mainly expressed in the uterus, prostate stroma, ovarian theca cells, Leydig cells in the testis, epididymis, mammary gland, and liver, whereas ERβ is expressed in prostate epithelium, testes, ovarian granulosa cells, bone marrow, and the brain. ERα promotes cell cycle progression, acting as ligand-dependent transcription factor.[164]

Selective ER modulators (tamoxifen, raloxifene) or degrader (fulvestrant) and aromatase inhibitors (anastrozole, exemestane)[165] are available.

ERα mutations are frequently observed in metastatic BrCa patients previously treated with aromatase

inhibitors[166] and are related to constitutive ligand-independent ER activation and resistance to hormonal therapies. Thus, *ERα* mutations detected in *BRCA*-positive BrCa may have important therapeutic implication.[167] *ERα* was found mutated in a patient with low-grade serous ovarian carcinoma who became resistant to aromatase inhibitor therapy after prolonged response.[168]

In conclusion, ESMO ranked *ERα* mutations in class 2A (Table 1) although ERα actionability is limited to ER-positive BrCa patients.

OTHER BIOMARKERS

PD-1/PD-L1

PD-1 and its ligand (PD-L1) constitute one of the most important nodes in tumor immune escape. PD-L1 is expressed in several cancers as well as in tumor-infiltrating immune cells; mutations in the *TTK* dual-specificity kinase and *PIK3CA* may affect PD-L1 expression.[169] Blocking PD-1/PD-L1 interaction enhances T-cell response[170] and for this reason anti-PD-1 moAbs pembrolizumab, nivolumab, and cemiplimab, and anti-PD-L1 moAbs atezolizumab, avelumab, and durvalumab have dramatically changed the management of several tumors, particularly in NSCLC and melanoma. Suppression of the PD-1—PD-L1 axis provided excellent results in classical Hodgkin lymphoma as well.[171] Atezolizumab added to nab-paclitaxel improves OS in triple-negative BrCa, more effectively in PD-L1-positive tumors.[172] Similar findings were observed with pembrolizumab and chemotherapy; pembrolizumab improves the pathologic complete response in the neoadjuvant setting, regardless of PD-L1 expression.[173]

Although with limitations, it can be concluded that PD-L1 expression represents the best predictive biomarker. Standardization of method validation for PD-L1 expression may provide a less variable definition of PD-L1 expression and cut-offs for selecting PD-L1 patients to receive anti-PD-1/PD-L1 treatments.

Tumor mutational load

Tumor cells harbor somatic mutations that contribute to their malignant phenotype. However, these mutations can lead to the production of neoantigens that may become more easily recognized by the immune system.[174]

Tumor mutational load (TML) has been associated with better responses to immune checkpoint inhibitors in melanoma, NSCLC, and HNSCC. Not limited to these tumors, high somatic TML might predict clinical benefit across diverse cancer types,[175] whereas no association was found in patients not treated with immune checkpoint inhibitors, highlighting the predictive, not prognostic, value of this biomarker.[175] A strong correlation between TML and ORR with anti-PD-1 or anti-PD-L1 was found in 27 tumor types.[176]

In conclusion, clinical evidence suggests that TML can be a reliable predictive biomarker of response to anti-PD-1/PD-L1 moAbs (Table 1). However, as for PD-L1 expression, the TML cut-off predictive of drug response may vary in different tumor types, suggesting the need for additional studies integrating TML with other parameters to refine predictions for improved patient selection.

Microsatellite instability

Genetic instability in short nucleotide repeats (MSI) is the result of abnormal DNA mismatch repair caused by a high mutation rate. MSI frequency is reported in CRC (13%), endometrial and gastric cancer (22%), HNSCC (3%), RCC (2%), and bladder cancer (1%). These figures are lower than those of patients that may respond to PD-1/PD-L1 inhibitors.[177] MSI-H tumors have durable responses, high ORR, and a statistically significant improvement in OS to PD-1 inhibitors. Nivolumab was approved for treatment of MSI-H metastatic CRC patients and pembrolizumab for any MSI-H or MMR-deficient solid tumor.[178,179] As clinical MSI testing is mostly performed in CRC and endometrial tumors, the prevalence of MSI in other cancer types is less described. The ability to detect MSI by approved liquid biopsy methods may allow a dynamic monitoring of drug response in different cancer types.[180]

In conclusion, MSI is the first approved tissue-agnostic biomarker for anti-PD-1 treatments, regardless of PD-L1 expression, and data suggest that the use of MSI can also be extended to other drugs of the same class (Table 1).

THE MOLECULAR TUMOR BOARD

The concept of MTB is strongly linked to the unique evolution of cancer treatments toward the discovery of actionable mutations that can also be druggable. Candidate patients are those with different types of cancers that either failed standard therapy or are expected to fail, those with rare tumors for which there are no/few standard options, and those with tumors of unknown primary origin.[181]

MTB is a group of oncologists, radiologists, pathologists, molecular biologists, geneticists, bioinformaticians, pharmacologists, pharmacists, bioethicists, and patient representatives (Figure 2) that provide support for the inclusion of patients in clinical trials or the use of off-label drugs.[182-184]

Each professional has a definite role: the clinician will select the patients suitable for discussion in the MTB; he/she will document the absence of standard lines of therapy, evaluate the risks/benefits of an experimental therapeutic option proposed by the MTB and its compatibility with previous therapies. The molecular pathologist will diagnose the molecular alterations, discuss their relevance, and, if necessary, suggest which additional tests should be conducted based on available methodologies. The radiologist will assess the extent of the disease and its progression, provide a comparative analysis of the imaging data, and select representative images to facilitate multidisciplinary discussion. The geneticist and molecular biologist with expertise in oncogenetics will evaluate the cases to be tested on germline DNA, and discuss their role and the risk of heredity. The clinical

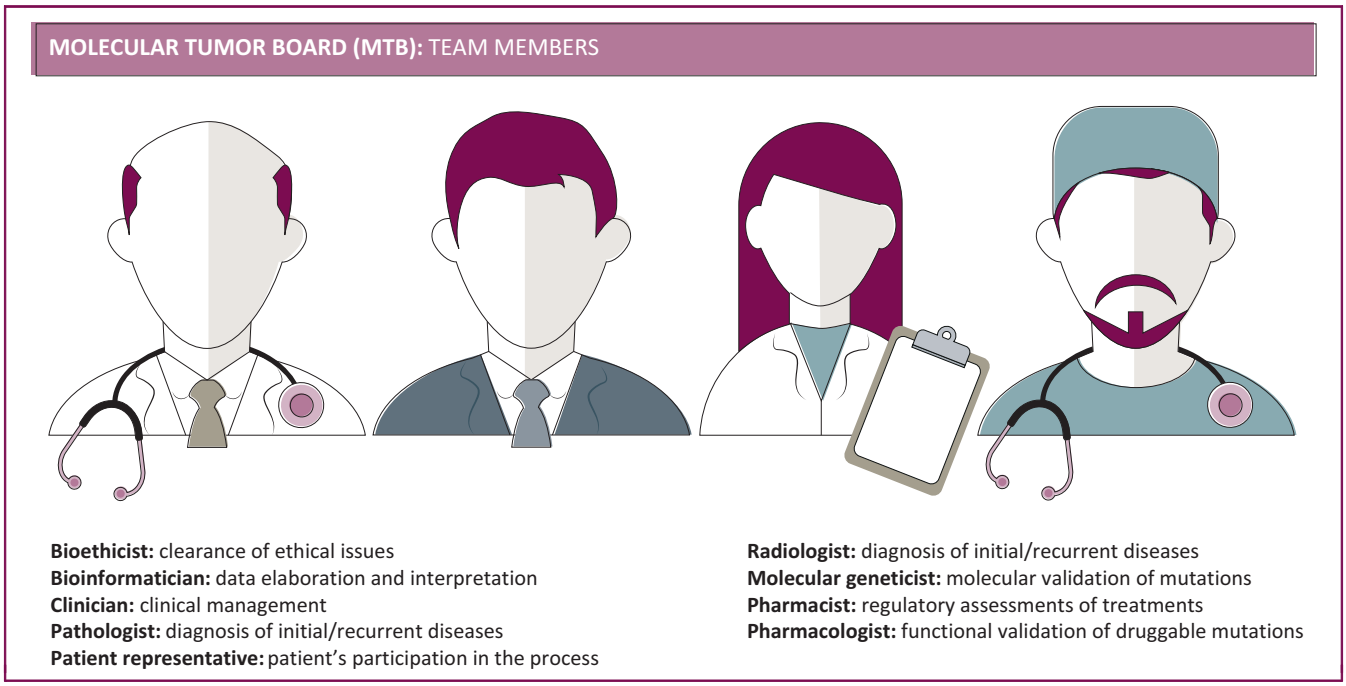

Figure 2. **Composition and function of the Molecular Tumor Board (MTB).**

pharmacologist will evaluate the patient's previous pharmacological history, perform molecular analysis of resistance mutations on liquid biopsy, discuss the congruence of molecular alterations with the candidate drug as well as the risk of adverse reactions or drug interactions, the latter in collaboration with the pharmacist who will assess the prescribability of specific treatments, according to local and national regulations, particularly when it comes to off-label drugs. The bioinformatician will analyze the molecular data using networks and computer systems integrated with public databases. Lastly, the bioethicist and patient representative are empowered to assess the ethical aspects associated with the use of experimental treatments and to communicate health care decisions to the patient.

Hospitals with experienced MTBs in the United States include the M.D. Anderson, Dana Farber Cancer Institute, and the University of California at San Diego while, in Europe, the Center for Personalized Cancer Treatment in the Netherlands and the Gustave Roussy Hospital in Paris, France, are worth mentioning.

The need for integrated professional skills can be exemplified by taking into account the complexity of supporting/evaluating precision medicine trials focused on specific cancer genetic alterations. The major challenges in biomarker-driven studies consist in understanding whether a driver mutation is druggable or actionable. An example of tumor classification based on the overall frequency of actionability has been reported in the AACR Project GENIE.[8] Criteria adopted for classification include tumors having alterations for which approved drugs are available (1 or 2A); that are level 1 or 2A in other tumor types (2B), for which clinical evidence for response to investigational therapies in the same disease does exist (3A); and that are level 3A in other tumor types (3B).[8] Actionability rate varies across different cancer types but, overall, the value stands at or above 30%.[8] OncoKB classifies oncogenic drivers into four levels of evidence based on whether genetic alterations are able to predict response to FDA-approved targeted drugs or investigational agents.[185] Finally, actionable mutations have been recently revised by the ESMO.[138]

In Figure 3 we graphically represent the workflow leading to MTB consultation, while in Table 1 we summarize the classification of druggable/actionable alterations.

Liquid biopsy is widely used to monitor several actionable mutations; however, only few tests, including detection of

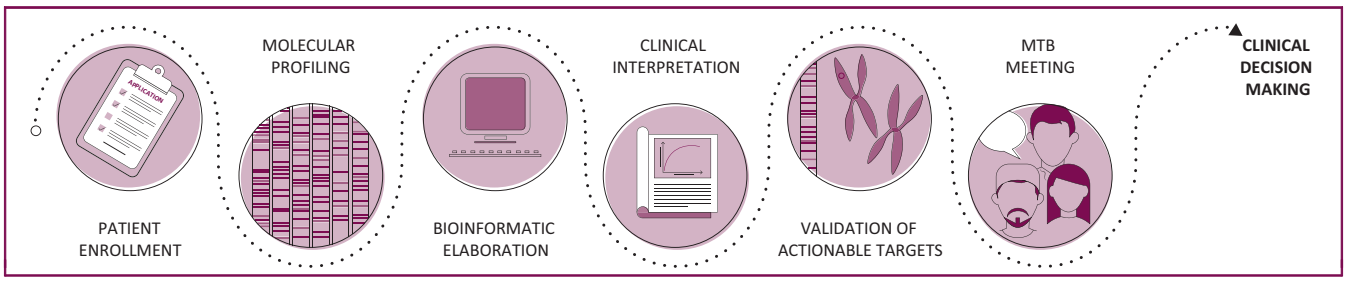

Figure 3. **Work flow—from patient enrollment to pharmacological treatment selection.**

EGFR mutations and ALK fusions in NSCLC, BRAF mutations in CRC, PIK3CA mutations in breast cancer, BRCA1-2 and ATM mutations in ovarian/prostate cancer and the MSI-H genotype (Table 1),[186,187] have been approved as Companion Diagnostics (CDx) by regulatory authorities, such as the FDA. Genomic instability may allow tumors to easily acquire new resistance mutations after initial response to targeted drugs. Liquid biopsy is an efficient way to perform a monitoring of drug response and scientific efforts should be focused to obtain validated tests.

Other important issues to be considered are study design and selection of the clinical settings and outcomes. For example, translational research studies are generally single-arm trials where the study drug is given to patients harboring specific genetic variants. The aim of these studies is to evaluate drug response in mutated versus nonmutated population.[8] Large-scale trials, such as the NCI-MATCH, require a wide network of investigators, an extensive collaboration with testing laboratories, and rapid enrollment of a large number of cancer patients.[66]

CONCLUSIONS

An increasing number of new targeted drugs demonstrated clinical benefits in multiple cancer types. The availability of new technologies (e.g. next generation sequencing) and approaches (e.g. liquid biopsy) allow clinicians to better select patients based on their genetic make-up. Therefore, in the era of precision medicine, integration of different professional skills is mandatory and the establishment of MTB may represent the most important asset to support clinicians in translating new scientific knowledge into daily clinical practice. Target-based classification is increasingly used to integrate the histology-based classification of tumors, which remains the backbone of cancer diagnosis and management.

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RD serves on the scientific advisory board and has consulting relationship with Ipsen, Novartis, Pfizer, Sanofi Genzyme, AstraZeneca, Janssen, Gilead, Lilly, Gilead, EUSA Pharma; and reports support for travel, accommodation, and expenses from Ipsen, and Sanofi Genzyme. SF serves on the scientific advisory board of, has consulting relationship with, and reports receiving support for travel expenses from Novartis, Teva, Roche, BMS, Lilly. MDR serves on the scientific advisory board and has consulting relationship with Ipsen, Novartis, Pfizer, Sanofi Genzyme, AstraZeneca, Pierre-Fabre, Janssen; and reports support for travel, accommodation, expenses from Ipsen, AstraZeneca, Sanofi Genzyme. APDT serves on the advisory boards of Roche, Bayer, Novartis, and reports receiving a travel grant from PharmaMar. VG serves on the advisory board and speakers' bureau of Lilly and Novartis (Advisory board and speakers' bureau), and reports receiving an institutional research grant from Roche. AP is an employee of Roche and has integrated access to data. SI, LL, LA, LB, GA, and PC have nothing to disclose.

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