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New Strategies in Personalized Medicine for Solid Tumors: Molecular Markers and Clinical Trial Designs

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Abstract

The delineation of signaling pathways to understand tumor biology combined with the rapid development of technologies that allow broad molecular profiling and data analysis, has led to a new era of personalized medicine in oncology. Many academic institutions now routinely profile patients and discuss them in personalized medicine tumor boards before making treatment recommendations. Clinical trials initiated by pharmaceutical companies often require specific markers for enrollment or at least explore multiple options for future markers. In addition to the still small number of targeted agents that are approved for the therapy of patients with histological and molecularly defined tumors, there is a broad range of novel targeted agents in development that are undergoing clinical studies with companion profiling to determine the best responding patient population. While the present focus of profiling are genetic analyses, additional testing of RNA, protein and immune parameters are being developed and incorporated in clinical research and are likely to contribute significantly to future patient selection and treatment approaches. As the advances in tumor biology and human genetics have identified promising tumor targets, the ongoing clinical evaluation of novel agents will now need to show if the promise can be translated into benefit for patients.

Background

Over the last decade, the delineation of signaling pathways to understand tumor biology has laid the foundation for the discovery of novel targets and development of multiple therapies for cancer. The identification of driver mutations and critical pathway dependencies, as well as genomic sequencing and other large-scale “-omics” approaches, have facilitated the discovery and development of novel targeted anti-cancer therapeutics, or at least provide the scientific rationale for their development. This increased molecular understanding of tumors has led to a new era of personalized medicine that has begun to influence common practice for oncologists beyond academic institutions.

The National Cancer Institute (NCI) defines Personalized Medicine, often also named “Precision Medicine”, as “A form of medicine that uses information about a person's genes,

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proteins, and environment to prevent, diagnose, and treat disease". Personalized medicine uses specific markers in patients' tumors to diagnose particular cancers or make treatment decisions. A specific marker may have prognostic significance for biological behavior or predict therapeutic outcome with a particular anti-cancer agent. This review will focus on predictive markers associated with tumors and not discuss host genetic factors that also can determine treatment and prognosis.

Traditionally, the site of tumor origin, together with histology, was used to make treatment decisions. This approach has been changed to include molecular tumor parameters. Markers presently used to guide decisions for personalized medicine treatment with targeted agents are either protein-based (immunohistochemistry (IHC)) or detecting genetic aberrations and are summarized in Table 1. For genetic aberrations, a range of methodologies, including Fluorescent in situ Hybridization (FISH) -tests, polymerase-chain-reaction (PCR), sequencing – nowadays often Next-Generation-Sequencing (NGS) of either multiple selected genes in parallel or whole exome sequencing – are used, in particular in early clinical trials or for exploratory purposes. These large panels of genes offer the opportunity not only to detect aberrations, for which treatment options already exist, but also to generate data on additional driver mutations or resistance pathways (1, 2). Treatment decisions may be based on the data when tests have been performed in Clinical laboratory Improvement Amendment (CLIA)-certified laboratories.

Anti-hormonal agents such as tamoxifen have been used for decades, initially without molecular profiling. Studies later correlated outcome with the expression of estrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR). The presence of ER, PR and AR not only categorizes breast and prostate cancers into different prognostic groups, but also determines treatment. Trastuzumab, a monoclonal antibody targeting human epithelial growth factor receptor-2 (HER-2) was approved for patient populations with a specific molecular profile, Her-2-overexpresing breast and gastric cancer (3-5). The first agent targeting a chromosomal translocation, imatinib, was originally approved for the treatment of Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia, based on inhibiting the Bcr-Abl tyrosine kinase (6). In 2008, based on the additional activity of imatinib to inhibit c-Kit, approval by the FDA for the treatment of adult patients with c-Kit (CD117) positive unresectable and/or metastatic Gastrointestitinal Stromal Tumors (GIST) followed (7, 8) The development of vemurafenib for advanced BRAFV600- mutated melanoma (9) and crizotinib for patients with NSCLC with ALK translocations (10) are other recent successes of therapies targeting molecularly defined tumor subtypes. Molecular profiling can also lead to a negative selection, as the retrospective studies showing consistent lack of benefit from the anti-EGFR antibodies cetuximab or panitumumab in CRC patients with KRAS codon 12/13 mutations led to the recommendation to restrict the use of these antibodies to patients with wild-type Kras tumors (11-14).

Lung cancer has become the prototype for genetically tailored cancer therapy. The remarkable advances in understanding molecular drivers in NSCLC together with the development of targeted agents allows classification of NSCLC on a molecular basis and molecular profiling has become routine practice in thoracic oncology. EGFR mutations were discovered in 2004 in parallel to the development of gefitinib, an EGFR tyrosine kinase

inhibitor (TKI), when retrospective studies revealed that patients with responses harbor exon 19 deletions or exon 21 point mutations (15, 16). This led to the use of the EGFR TKIs gefitinib and erlotinib as initial treatment for patients with these mutations. The discovery of EGFR mutations and the large benefit of targeted treatment has boosted profiling and the search for novel targets. The development of crizotinib to treat patients with ALK fusions, detected by a FISH-assay, highlights one of the outstanding successes in lung cancer with rapid development of a treatment (17). More recently the additional activity of crizotinib in patients with ROS-fusions (18, 19) was discovered and patients with RET-fusions are beginning to be treated with the RET inhibitors vandetanib and carbozantinib (20-24).

While these targeted therapies have brought significant improvements, all patients eventually develop therapeutic resistance. Multiple resistance mechanisms have been characterized, such as secondary mutations preventing inhibitor binding, EGFR or HER2 gene amplifications, HGF/Met pathway activations as well as PI3K and BRAF mutations (25, 26). Multiple resistance mechanisms have also been identified in patients with ALK fusions who progress on crizotinib. These include ALK mutations, copy gain number and mutations in alternative pathways, including EGFR mutations. Second and third generation inhibitors of EGFR and ALK, such as AZD9291 with activity against EGFRT790M and alectinib or ceritinib, especially active against the L11986M ALK mutation that confers resistance to crizotinib, are now in development with initial promising data (17, 27-32).

Multiple de-regulated pathways have been identified across a range of tumor types, which could potentially be targeted by novel agents (summarized in Table 2). However, often several genetic aberrations are found in the same tumor and it is not always clear which are driver mutations, which are secondary changes and which are the determinants of inherent or acquired resistance. Moreover, mutations that clearly act as driver mutations in one tumor type may not be of similar relevance in another tumor. For example, malignant melanoma patients with BRAF V600E mutations respond to treatment with vemurafenib, (33) whereas patients with colorectal cancer, that harbor the same mutation, seem to derive little benefit from BRAF inhibitors due to complex mechanisms that include a feedback loop that increases EGFR expression (34). There are multiple studies ongoing testing these hypotheses. Studies with preliminary results that are encouraging include PI3K/AKT/mTOR inhibitors in PIK3CAmt- or PTEN deficient cancers (35).

On The Horizon

Many cancer centers now profile patients by genetic testing, RNA expression profiling, or protein analyses and use the obtained data to direct patients to clinical trials at their centers or elsewhere (36, 37). Genetic profiling is booming and molecular profiling is discussed in multi-disciplinary tumor boards and contributes to treatment recommendations. Some academic cancer centers now hold a weekly Precision Tumor Board in which oncologists together with radiologists and molecular pathologists present cases. The multi-disciplinary team, that also includes basic and translational scientists, surgeons and nurses, discusses the cases and potential treatment options. Presently, molecular profiling is mostly limited to genetic aberrations (mutations, translocations, fusions, copy number variation (CNV)), but it is planned to extend the profiling to include RNA-, and immune-profiling (Figure 1). While

currently genetic profiling is only performed for patients for whom additional data are critical to guide treatment, it is envisioned that in the near future all patients treated at academic cancer centers will have a diagnostic tumor sample analyzed for genetic aberrations, and with repeat-biopsy programs in place, ideally also at progression. The ultimate goal of the profiling is to find the best available treatment for the patient, mostly by enrollment in a clinical trial, if such a trial exists. There is an urgent need for more studies with molecularly targeted agents that are open for patients across tumor types to investigate if these treatments can benefit other patient populations.

Several institutions and companies have launched trials, that assign patients based on molecular profiling of tumors in specific cancer types (BATTLE I and II) (38), but also independent of cancer type. These studies include observational studies, as well as non-randomized and randomized studies (2, 39-41). Non-randomized studies building on the ability of academic cancer centers to perform molecular profiling in CLIA certified laboratories have been initiated in 2013 by pharmaceutical companies making a number of agents available for use in molecular defined patient populations. These include agents for which safety data already exist and a Phase II dose is defined, and exclude patient populations for which the drugs are either already registered or for which dedicated randomized studies exist or populations where a lack of benefit for the agent was already observed. For example, the Novartis SIGNATURE studies offer independent trials with investigational agents from a pharmaceutical company for patients with a specific molecular profile (42). These agents would otherwise not be available for patients with many tumor types, as specific studies in all tumor types do not exist. The NCI is planning to open a study of a similar type in 2014, NCI-MATCH, which is expected to include agents from multiple companies (43). For the NCI-MATCH studies, genomic profiling will be performed by a consortium of NCI-selected CLIA-certified laboratories using NGS of a defined number of genes as the basis for enrollment. The arms of the NCI-MATCH study are still under discussion. It is expected to include agents from multiple companies under NCI sponsorship and will validate the proposed broad sequencing platform. The SHIVA study randomizes patients with a particular molecular abnormality with any type of cancer between the matched agent and conventional cytotoxic therapy, with crossover on progression (39). The SHIVA study is different to the other two mentioned studies in that it has SOC comparator arms for each newly tested agent and will therefore collect data on the outcome of SOC therapies in molecular segments. More studies of this type with agents in development would be of high interest, but are difficult to initiate and coordinate if they involve multiple companies. The results of these ongoing studies are likely to identify additional patient populations for targeted therapy and hopefully will aid registration for additional indications. Data collection is critical for the future direction of personalized medicine and may trigger additional basic research to fully understand the contributions of newly discovered mutations to tumor development and progression.

Is testing for certain mutations sufficient or should broad testing be applied to all samples? Single mutation or small panel testing has the clear advantage of requiring smaller amounts of tissue, is less costly and interpretation of data is simpler and hence often quicker. While there are only a few tests that clearly direct patient treatment at this time (see Table 1), only broader testing will facilitate better understanding of tumor drivers and mechanisms of

resistance critical for future direction. Multiplexing also requires less tissue than multiple single tests. The latter is becoming an increasing problem for Phase I trials, where companies require large amounts of tissue for testing to evaluate eligibility that exhaust archival diagnostic tissue resulting in patients requiring new biopsies or even deprives them of enrollment if a new sample cannot be obtained.

Advanced technology has revealed intra- and inter-tumor heterogeneity at protein, genetic and epigenetic level (44, 45). Genetic analyses, RNA- and protein - profiling of primary carcinomas and metastases from the same patients with renal carcinomas showed a large heterogeneity with most detected genetic aberrations not consistent between lesions and tumor regions that confirm that multiple clonal subpopulations exist within a single lesion (46, 47). In contrast, genetic analyses of colorectal and lung cancer lesions showed more concordant data for a limited gene set (48, 49). Indeed, the effectiveness of available targeted treatments for advanced cancer patients such as gefitinib in EGFRmt lung cancer and cetuximab or panitumumab in KRASwt CRC has largely been demonstrated in clinical trials that identified the mutations from archival diagnostic biopsies. In light of the heterogeneity, it is questionable, if a single archival biopsy taken for diagnostic purposes in early stages of the disease is sufficient as a sample for molecular profiling to guide treatment. Even if a new biopsy is available for analysis, is one sample sufficient, if multiple lesions may have a very different molecular profile? How many areas of a single tumor need to be biopsied to obtain comprehensive information of the drivers of the tumor in a patient? Answers to these questions are urgently needed.

Given the emergence of resistance as described above, it is expected that future patients' tumors will need to be profiled at several times during treatment in order to determine best treatment options. Indeed, some academic cancer centers have repeat-biopsy programs in place, pursuing new biopsies when patients progress on targeted treatment, in particular with EGFR or ALK inhibitors. How realistic are multiple longitudinal biopsies for a majority of cancer patients across tumor types and do we urgently need to increase our efforts to further explore other technologies that may be able to assess tumor mutations without multiple longitudinal biopsies or parallel biopsies of different lesions?

To minimize invasive procedures, the analysis of cfDNA or CTCs should be explored further to evaluate if these technologies can replace multiple biopsies for molecular analysis, especially, as patients move through successive lines of treatment. Initial results are promising (50-52). Is genetic profiling really enough? How do we approach the many targets for which treatment options do not yet exist, including the ones that are presently considered un-druggable, like TP53 and KRAS (53-56). Do we need broader molecular profiling that includes other endpoints to strengthen scientific understanding and other selection methods, especially if they can be applied to samples other than tumor biopsies?

Serum proteins have been established as general prognostic factors, for example PSA levels in prostate cancer patients. CEA is measured as a tumor marker across multiple tumor types and high levels have been shown to correlate with poor prognosis (57-59). Attempts to identify serum proteins as predictors for response to targeted agents so far have had limited success (60, 61), but this has not been assessed broadly. Further serum marker studies in

clinical trials should be encouraged, especially, if tumor samples at baseline of these trials are available and could be compared to serum assays.

Other areas presently explored are RNA profiling (mRNA and miRNA), epigenetic and immune profiling (62-64). RNA analyses will strengthen the understanding of de-regulated signaling pathways in cancer that genetic profiling alone may not reveal and may lead to novel hypotheses for targets. Immune profiling will become important as new therapies, especially immune check point therapies demonstrate striking activity is several cancer types.

While great progress has been made towards molecular profiling for personalized cancer therapy, it is expected that with rapidly developing technology, molecular determinants other than genetic aberrations may emerge that will contribute to treatment decisions. The next five years will decide if personalized medicine will become standard practice across all tumor types and if this will revolutionize treatment options for greater survival benefit for cancer patients.

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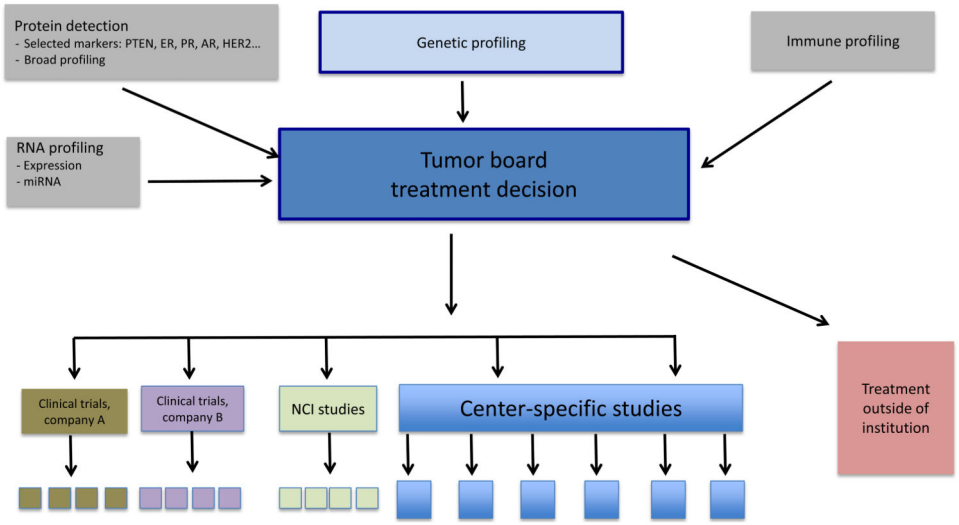

Figure 1. Academic Medical Center Precision Medicine Tumor Board Model

Table 1

Molecular selection markers for approved anticancer agents

Target	Cancer	Variation type	Marker	Drug	test
EGFR	Lung cancer	Mutation	Predict benefit to EGFR TKIs	Erlotinib Gefitinib	DNA
ALK	Lung Cancer	Rearrangement	Predict response to ALK-inhibitors	Crizotinib	FISH
ROS	Lung Cancer	Rearrangement	Predict response to TKIs	Crizotinib	FISH
RET	Lung Cancer	Rearrangement	Predict response to TKIs	Vandetanib	FISH
BRAF	Melanoma	Mutation	Predict response to BRAF-inhibitors	Vemurafenib Dabrafenib	DNA
KRAS	CRC	Mutation	Predict lack of response to anti-EGFR antibodies	Panitumumab Cetuximab	DNA
HER2	Breast Cancer Gastric Cancer	Amplification Overexpression	Predict response to anti-HER2 antibodies	Trastuzumab Lapatinib Pertuzumab	FISH, IHC
KIT	GIST	Mutation	Predict response to c-Kit inhibitors	Imatinib	IHC
Estrogen receptor	Breast Cancer	Overexpression	Predict response	Examestane Fulvestrant Letrozole Tamoxifen	IHC
Progesterone receptor	Breast Cancer	Overexpression	Predict response	Examestane Letrozole	IHC

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Table 2

Genetic aberrations as putative predictive biomarkers for anticancer agents

Target/Pathway	Aberration type in solid tumors	Disease examples	Putative or proven drugs	Examples for drugs in clinical development	References
EGFR	Mutation Amplification	Lung cancer GBM	EGFR inhibitors	Erlotinib Gefitinib Afatinib AZD9291	(15, 16, 25, 26, 30)
HER2 (ERB2)	Mutation Amplification	Breast cancer Gastric cancer Lung cancer	ERB2/ ERB3 inhibitors	Lapatini Neratinib Trastuzumab Trastuzumab-emtansine	(4, 5)
ALK	Rearrangement Mutation	Lung cancer Neuroblastoma CRC	ALK inhibitors	Crizotinib Ceritinib Alectinib	(10, 22, 28, 29, 65, 66)
RET	Rearrangement Mutation	Thyroid cancer Lung cancer	RET inhibitors	Vandetanib Carbozantinib	(19, 20, 23, 67)
ROS1	Rearrangement	Lung cancer	ROS1 inhibitors	Crizotinib	(18, 19)
DDR2	Mutation	Lung cancer	DDR2 inhibitors	Dasatinib Nilotinib	(68, 69)
FGFR1-4	Amplification Mutation	Lung cancer Gastric cancer Breast cancer Bladder cancer	FGFR inhibitors	Ponatinib Dovitinib BGJ398 AZD4547	(70, 71)
MET/HGF	Mutation Amplification	Lung cancer Gastric cancer CRC HCC RCC	Met inhibitors	Onartuzumab Crizotinib Foretinib INC280	(72-74)
KIT	Mutation	GIST Mastocytosis Melanoma	Kit inhibitors	Imatinib Nilotinib Sunitinib Dasatinib Ponatinib	(7, 8)
PDGFRA and PDGFRB	Mutation Translocation	GIST Sarcoma GBM Leukemia Dermatofibrosarcoma protuberans	PDGFR inhibitors	Imatinib Sunitinib Ponatinib	(8, 75)
KRAS, NRAS, HRAS (RAS-RAF-MEK)	Mutation	Most cancers, including CRC, Lung cancers	Mek inhibitors	Trametinib Selumetinib	(76)

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Target/Pathway	Aberration type in solid tumors	Disease examples	Putative or proven drugs	Examples for drugs in clinical development	References
BRAF (RAS-RAF-MEK)	Mutation	Melanoma CRC HCC	Braf inhibitors Mek inhibitors	Vemurafenib Dabrafenib Trametinib Selumetinib	(76, 77)
PI3KCA (PTEN/PI3K AKT/mTOR)	Mutation Amplifcation	Multiple, including: Breast Cancer CRC, GBM Lung Cancer Endometrial	PI3K inhibitors AKT inhibitors	BKM-120 BEZ235 BYL719 GDC0941 GDC0032 MLN1117 AKT inhibitors- see below	(78, 79)
PIK3R1 (PTEN/PI3K AKT/mTOR)	Mutation	Endometrial cancer CRC	PI3K inhibitors	PI3K inhibitors- see above	(79)
AKT1-3(PTEN/PI3K/AKT/mTOR)	Mutation Amplification	Breast cancer CRC Meningeal cancer Urinary tract cancers Endometrial cancer	PI3K inhibitors AKT inhibitors	GDC0086 MK2206 AZD5363 PI3K inhibitors- see above	(78-80)
PTEN (PTEN/PI3K/AKT/mTOR)	Deletion Mutation	Most cancers, including breast cancer Lung cancer CRC	PI3K inhibitors AKT inhibitors	PI3K and AKT inhibitors- see above	(78-81)
mTOR (PTEN/PI3K/AKT/mTOR)	Mutation	Endometrial cancer RCC CRC Lung cancer	mTOR inhibitors	Everolimus Temsirolimus MLN128 AZD2014 GDC00980 BEZ235	(79, 82, 83)
TSC1/2 (PTEN/PI3K/AKT/mTOR)	Mutation	Tuberous sclerosis Urinary tract cancers Endometrial cancer Cervical cancer HCC, CRC	mTOR inhibitors	mTOR inhibitors-see above	(79, 84)
LKB1 (PTEN/PI3K/AKT/mTOR)	Mutation	Cervical cancer Small intestine cancer Lung cancer Skin cancer	mTOR inhibitors	mTOR inhibitors- see above	(79)
SMO, PTCH1 (Hedgehog)	Mutation	Basal cell carcinoma Medulloblastoma Meningioma Breast cancer	Hedgehog inhibitors	Vismodegib	(85, 86)
MDM2	Amplification	GBM Sarcoma	MDM2 inhibitors/ antagonists disrupting p53-MDM2 interaction	RG7388	(53, 54)
P53	Mutation	Most tumors	P53 activators		(53, 54)

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Target/Pathway	Aberration type in solid tumors	Disease examples	Putative or proven drugs	Examples for drugs in clinical development	References
NOTCH	Mutation Rearrangement	Breast cancer Lung cancer Ovarian cancer GBM H&N cancer	Gamma-secretase inhibitors ABs to Notch receptors or ligands	MK0752 PF03084014 Demcizumab OMP59R5 OMP52M51 Enoticumab	(87, 88)
CDKS	Amplification Mutation Rearrangement	Sarcoma Melanoma GBM	CDK inhibitors	Flavopiridol Palbociclib	(89)
CHK1/2	Mutation	Multiple tumors, including: CRC Gastric cancer Endometrial cancer Breast cancer	CHK inhibitors	RG7741 LY2606368	(89)
AURKA (Aurora Kinases)	Amplification	Multiple tumors	Aurora kinase inhibitors	Alisertib	(89, 90)
ATR	Mutation Deletion	Gastric cancer Breast cancer Endometrial cancer	ATM inhibitors PARP inhibitors	No ATM inhibitors in clinical development PARP inhibitors- see below	(89, 91)
ATM	Mutation Deletion	Multiple tumors, including Breast cancer	ATR inhibitors PARP inhibitors	VX970 PARP inhibitors- see below	(89, 91)
BRCA1/2	Mutation	Breast cancer Ovarian cancer	PARP inhibitors	Olaparib Veliparib Rucaparib BMN673	(92, 93)