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Targeted therapy for metastatic melanoma: From bench to bedside

Malignant melanoma is well known for its aggressive clinical behavior, propensity for lethal metastasis and therapeutic resistance. However, in the last decade, considerable excitement has been generated by the identification of genetic mutations in various components of signaling pathways involving melanoma initiation and progression, particularly those involved in the MAP and PI3 pathways. Most recently, clinical trials of pharmacological targeting of relevant molecular targets have demonstrated dramatic response even in patients with late-stage melanoma.

The emerging insights into the mechanisms of activation and negative regulation of innate and adaptive immunity to tumors have provided another breakthrough in melanoma therapy. A new family of immune-based agents of monoclonal antibodies that exert their functions by tampering with immune system cell molecules causing an enhancement of antitumor immune responses has entered clinical trials. In general, these new antitumor agents are designed to break down the barriers to tumor tolerance/immunity. This new group of agents holds promise for at least additive effects to conventional therapies, as well as signal transduction pathway targeted therapies.

Targeting signal transduction pathways

Several key genetic lesions governing melanoma initiation and progression have been identified, the earliest and most common being a point mutation (T1799A) in the *BRAF* proto-oncogene, which is detected in approximately 60% of metastatic melanoma. *BRAF*^{T1799A} encodes *BRAF*^{V600E}, a constitutively active protein serine kinase that elicits sustained activation of the *BRAF* → *MEK1/2* → *ERK1/2* MAP kinase pathway.

In addition to *BRAF*, *RAS* oncogene (rat sarcoma viral oncogene homolog) is another constituent of the MAP kinase pathway. *RAS* mutations (in one of three isoforms) are found in approximately 20% of metastatic melanoma. *RAS* is capable of turning on several downstream pathways, including *BRAF* and other components of MAP kinase pathways, PI3 kinase pathway, and the RAL-GDS pathway. In general, if a *RAS* mutation is present, there will be no *BRAF* mutation. However, the combination of mutated *BRAF* and silencing of *PTEN* expression is common in human melanoma (~20%). Dankort and colleagues have demonstrated in a preclinical model that "*BRAF*^{V600E} cooperates with *PTEN* loss to induce metastatic melanoma."

The prevalence of *RAS*/*RAF* alterations in human cancer has prompted significant efforts in the development of drugs targeting the MAP kinase pathway. Many of these are currently in clinical trials in patients with metastatic melanoma. Studies with the broad spectrum *RAF* inhibitor sorafenib (Nexavar, Bayer) as a single agent in patients with *BRAF* mutated melanoma have proved disappointing. What was unclear from these studies was whether the lack of efficacy was because *BRAF* was not a critical target or because of incomplete blocking of *BRAF* by sorafenib.

Since 2005, several *BRAF* inhibitors have entered clinical trials. These inhibitors are grouped in two categories: *BRAF* selective inhibitors, and broad spectrum multiple kinases inhibitors with high potency against *BRAF*.

BRAF inhibitors

PLX4032 (Plexxikon, also known as RO5185426) is a selective *BRAF* inhibitor and is the first of its kind tested in advanced melanoma. A response rate of 70% in 32 *BRAF* mutated melanoma patients was reported in the phase 2 study. In general, PLX4032 is well tolerated and most common toxicities include mild-to-moderate skin rash, sun sensitivity, fatigue, arthralgia and keratoacanthoma. Currently, there are two ongoing PLX4032 trials.

The first is a phase 2 study of PLX4032 as a single agent in *BRAF* mutated melanoma patients who have failed standard therapy for metastatic disease. This study will hopefully confirm the high response rates observed in previous phase 1/2 studies. The second is a phase 3 trial comparing PLX4032 with dacarbazine (standard

chemotherapy) in chemotherapy-naïve patients with *BRAF* mutated metastatic melanoma. Seven hundred patients will be enrolled; the primary endpoint is OS.

Another *BRAF* selective inhibitor is GSK2118436 (GlaxoSmithKline). This drug has already shown promising antitumor activity in the phase 1 portion of a study. The phase 2 portion is ongoing. The impressive high level of antitumor activity of *BRAF* selective inhibitors indicates that both PLX4032 and GSK2118436 have single-agent activity; *BRAF* is an important target in melanoma.



Wen-Hwa

Currently, there are at least two nonselective *BRAF* inhibitors. XL281 (Bristol-Myers Squibb) and RAF265 (Novartis) are in phase 1 testing. Results are expected in the near future.

MEK is a kinase and is immediately downstream of *BRAF*. It is never mutated in cancer but is activated by *BRAF* and, in turn, activates the rest of the MAP kinase pathway. In the laboratory, MEK inhibitors have shown activity in a number of *BRAF* mutated cancers. Currently, there are many MEK inhibitors in clinical trials.

AZD6244 (AstraZeneca) is a MEK inhibitor that has been evaluated most extensively in melanoma. A phase 2 study comparing AZD6244 with temozolomide (oral chemotherapy) has found an objective response rate of 12% among 45 *BRAF*-mutated patients. However, patients in this study who received temozolomide had a similar response rate and

Melanomas from acral lentiginous, mucosal and chronic sun-damaged sites frequently harbor activating mutations and/or increased copy number in the *KIT* tyrosine kinase receptor gene, which are very rare in more common cutaneous melanomas. Multiple case reports and early observations from clinical trials suggested that targeting mutant *KIT* with small molecule *KIT* inhibitors such as imatinib (Gleevec, Novartis) and/or dasatinib (Sprycel, Bristol-Myers Squibb) is efficacious.

Although the dramatic clinical activity of *BRAF* selective inhibitors is a major breakthrough in the treatment of this disease, there are many hurdles to overcome to optimize this targeted therapy approach. Many of the patients who initially responded to PLX4032 have subsequently progressed with a median duration of response of approximately 8 months. The mechanisms that cause resistance are largely unknown.

Recently, a number of preclinical studies have demonstrated that *BRAF* inhibitors activate MEK and MAP kinases in melanoma cell lines with wild-type *BRAF*, including cell lines with mutant *NRAS*. These studies suggest at least one potential mechanism of resistance is through continued activation of the RAS-RAF-MEK-ERK signaling pathway. The combination agents that target multiple components of this pathway have great potential to overcome drug resistance. Several ongoing clinical trials using the combination of *BRAF* and MEK targeted agents will be able to test this hypothesis.

Targeting tumor immunity barriers

Since the discovery of monoclonal antibodies in the late 1970s, it has become clear that these antibodies, which are of defined specificity and can be produced in large amounts, had potential for the management of various diseases, including malignancies.

The key property of antibodies to be used as therapeutic tools is their behavior as high-avidity ligands to protein or glycoprotein. Most recently, a new group of monoclonal antibodies that enhance the cellular immune response against cancer have entered clinical trials. These agents bind molecules on the surface of immune system cells. They either provide activating signals to lymphocytes and antigen presenting cells or block the action of receptors that normally down-regulate the immune response.

A humanized monoclonal antibody (MDX-010, Medarex) against cytotoxic T-lymphocyte antigen 4 (CTLA-4) is the first to reach clinical trials. CTLA-4 is only expressed on the cell surface of activated T cells and regulatory CD4+ CD25+ T cells. In murine models, systemic treatment with transplantable immunogenic colon carcinoma cells with anti-CTLA-4

monoclonal antibodies induced complete tumor regression of established tumors through an immune response found to be critically dependent on the activity of cytotoxic T lymphocytes.

Various phase clinical studies have been conducted on the two anti-CTLA-4 monoclonal antibodies, ipilimumab (Bristol-Myers Squibb) and tremilimumab (Pfizer), as monotherapy, in combination with vaccines or other immunotherapies, in combination with chemotherapies. Blockade by the T-cell inhibitory molecule CTLA-4 results in antitumor response with overall response rates from 10% to 20%. Most adverse events involve autoimmune toxicities, such as dermatitis, uveitis, colitis/enterocolitis, hepatitis and hypophysitis.

4-1BB (CD137) is a surface glycoprotein that belongs to the TNF receptor family. It is expressed by activated, but not resting, T and NK cells. A humanized anti-4-1BB monoclonal antibody (Bristol-Myers Squibb) has been tested in clinical trials. However, the phase 2 study in refractory melanoma was discontinued in May 2009 due to unusually high incidence of grade-4 hepatitis.

Programmed death 1 (PD-1) and its ligands, PD-L1 and PD-L2, deliver inhibitory signals that regulate the balance between T cell activation, tolerance and immunopathology. In vivo studies have shown B7-1 (CD80) is also a binding partner for PD-L1, and their interactions can lead to bidirectional inhibitory response in T cells.

PD-L1 is expressed on many tumors including melanoma and is a component of the immune suppression by the tumor microenvironment. Phase 1/2 experience of the anti-PD-1 monoclonal antibody, MDX-1106 (Medarex, Ono-4538), in refractory or relapsed malignancies was presented at the 2009 ASCO Annual Meeting. Clinical activity against melanoma was observed and, more importantly, no MDX-1106 related severe adverse events were noted.

In 2009, at M.D. Anderson Cancer Center, we participated in a phase 1 study of anti-PD-L1 monoclonal antibody (MDX-1105, Medarex) in refractory metastatic melanoma. MDX-1105 has been tolerated by all patients. Most adverse events were mild and were related to inflammatory responses in the tumors, not immune-related toxicity. Clinical responses were observed at all dose levels (1 mg/kg to 10 mg/kg every 2 weeks). Durable partial responses and stable disease were noted in patients whose disease had progressed after at least one, and as many as five, prior systemic therapies. Based on the low toxicity and impressive clinical activity, a phase 2 study of MDX-1105 in advanced melanoma is warranted.

In summary, the treatment of metastatic melanoma is changing rapidly due to the great success in translational research from bench to bedside. Although such studies, to date, have focused on the treatment of advanced metastatic disease, approaches of targeting signal transduction pathway, as well as targeting tumor immunity barrier, hold great promise for the development of preventive strategies and personalized therapies in malignant melanoma.

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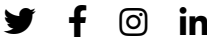
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