

ASCO '08

» A Look at the Progress in 3 Different Cancer Types

Rather than try to review the overwhelming amount of science at ASCO '08, we picked 3 tumor types that seem to be getting a lot of attention and present, here, some of the findings and progress discussed at this year's meeting.

MELANOMA: PURSUING AN UNMET CLINICAL NEED

Despite years of clinical trials involving cytotoxics, DNA-damaging and anti-microtubule agents, as well as immunomodulatory therapies, the natural history of advanced melanoma has changed very little. For patients who develop progressive disease, the two FDA-approved agents—interleukin-2 and dacarbazine (DTIC)—produce responses in just 15% of patients.

As discussant of the Melanoma Highlights at this year's ASCO, Jeffrey S. Weber, MD, Head of the Melanoma Center of Excellence at H. Lee Moffitt Cancer Center, Tampa, Florida noted that melanoma truly qualifies as an "unmet need" in oncology. "Melanoma is the malignant histology that gives oncology a bad name," he commented. The field is "a work in progress," he added, though based on ASCO presentations he now sees "a significant glimmer of hope for new treatments on the horizon."

Much of the hope has been pinned on the anti-CTLA4 antibodies ipilimumab [BMS; Medarex] and tremelimumab [investigational; Pfizer]. Several single-arm, open-label studies reported at ASCO showed 1-year survival with ipilimumab to range from 47% to 60%, often in highly refractory patients. In some chemotherapy-naive patients with advanced disease, survival up to 5 years was observed.

Based on the FDA's request for control-arm data and overall survival as an endpoint, findings from the registrational studies in the second-line setting (previously submitted to the FDA) will be incorporated into a Phase 3 first-line trial comparing ipilimumab alone

to ipilimumab plus dacarbazine. Enrollment has been completed, and BMS is discussing an amendment of the endpoint (to overall survival) with the FDA.

The news for tremelimumab was not as good. While it produced stable disease in some patients, the agent failed to show improvement in overall survival compared with standard therapy, and the study was stopped early due to treatment futility. Pfizer indicates they will continue to study tremelimumab primarily in other tumor sites.

A death knell was also sounded for the adjuvant ganglioside GM2-KLH21 vaccine [Progenics] after negative, and potentially, even harmful results were reported by a European cooperative group (EORTC 18961). A Progenics spokesman told OBR, "I don't think anyone will be developing this compound now." But the GM-CSF-encoding oncolytic virus OncoVex [Biovex], when directly injected into tumors, produced a 32% response rate (even in distant metastases) and durable responses. Findings with the tyrosine kinase inhibitor axitinib [investigational; Pfizer] were also impressive in a single-agent trial, with a median survival of 13 months in an unselected population.

New Focus of Drug Development and Melanoma Subtypes

Progress has not occurred without fits and starts. The focus of drug development for advanced melanoma has traditionally been on the Ras/Raf/mitogen-activated protein (MAP) kinase cascade, but clinical trials of agents targeting this pathway have been disappointing. Recently, however, the Raf kinase inhibitor sorafenib [Nexavar; Onyx Pharmaceuticals] was shown to double the time to disease progression when given with dacarbazine.

Attention has turned to other approaches. Recently, the molecular alterations within melanoma cells have become better understood. Two categories to target include metabolic enzymes expressed in the tumor microenvironment, and developmental signaling pathways active in aggressive tumors. Strategies to interfere with these signals are poised for translation into the clinic, said Thomas F.



By Caroline Helwick

Gajewski, MD, PhD, Associate Professor of Pathology and Medicine, University of Chicago, who discussed novel pathways at an ASCO educational session.

Factors involved in metabolic alterations in the microenvironment, and possible therapeutic targets, include inducible nitric oxide synthase (iNOS), indoleamine-2,3-dioxygenase (IDO), and arginase. For example, high expression of iNOS protein seems to be a negative prognostic factor for survival (and a possible biomarker); therefore, interfering with nitric oxide might be beneficial. Investigators at ASCO showed that by “quenching” nitric oxide, they could overcome resistance to apoptosis.

As for the other approach—elucidating the developmental processes active in aggressive melanomas—Dr. Gajewski named the Notch, Wnt, and Nodal pathways as prime targets. “Inhibition of these pathways in preclinical models has shown important effects,” he reported.

Undoubtedly, multiple classes of agents will be needed to make an impact on melanoma, according to Dr. Gajewski. “My sense is that melanoma is not one disease, but a disease with many molecular subtypes.”

For example, c-KIT mutations, which are associated with gastrointestinal stromal tumors (GIST), are observed in 20% of the 10% of melanoma patients who have acral lentiginous melanoma (involvement of the palms, soles, nails). There are anecdotal reports that imatinib [Gleevec; Novartis], which is effective in GIST, can produce major responses in this molecular subtype.

“I believe our mission is to define these subtypes and determine which patients will respond to the individual therapeutic approaches,” he said.

Melanoma and Advances in Biomarkers

Elizabeth Grimm, PhD, Professor of Experimental Therapeutics at the MD Anderson Cancer Center, University of Texas, Houston, agreed with this emerging concept of subtypes.

“As the reality of targeted therapy and personalized medicine advances in melanoma, I predict that several molecularly definable subclasses of patients will be grouped by tumor and genetic biomarker signatures for prognosis as well as treatment options. Biomarker development is the key for achieving these goals in a rational manner,” she said.

But while a PubMed search lists 5,000 citations for “human melanoma biomarkers,” only serum lactatedehydrogenase (LDH) serves as a real marker. In a summary of ASCO studies, Dr. Grimm reported that certain microRNAs were expressed in melanoma cell lines, problematic pigmented lesions and melanoma primaries, but they lacked clear diagnostic value. Loss of the PP2R3B gene on Xp22 in females and Yp11 in males was associated with melanoma and may be a newly identified melanoma tumor suppressor. Elevations of S100B in the plasma of advanced patients added significant and independent value to LDH and could become a useful marker.

BRAIN TUMORS: A CHANGING LANDSCAPE

The treatment of malignant glioblastoma multiforme, the most aggressive of brain tumors, is no “home run” but the once-dismal prognosis has at least improved with temozolomide, [Temodar; Schering Plough]. The oral alkylating agent, unlike other agents, crosses the blood-brain barrier and enhances the response to radiotherapy. The combination has improved median survival by approximately 3 months and doubled the 2-year survival rate to 26%. Now, at 5 years, 10% of patients on the combination remain alive.

“We have improved long-term survival in a subset of patients, and we have established a standard of care for newly diagnosed glioblastoma,” said Mark Gilbert, MD, of University of Texas MD Anderson Cancer Center, Houston, Texas. [cont. on pg 36 >>](#)

ASCO '08

Investigators have further determined some patients do even better, specifically those with inactivation of the *MGMT* gene that causes resistance to chemotherapy and radiation. At 4 years (in an updated analysis) 22% of patients with inactivated *MGMT* were still alive after temozolomide plus radiotherapy. “This is previously unheard of in the field,” noted Dr. Gilbert.

Recent studies have shown that *MGMT* can be inactivated and resistance “depleted” by giving temozolomide continuously over 3 weeks. This is expected to enhance the treatment effect, a hypothesis that is being tested in RTOG 0525. With nearly 1200 patients enrolled, this is the fastest accruing and largest brain tumor trial ever conducted.

In other studies with temozolomide, a vaccine developed by Avant Immunotherapeutics Inc. showed promise in clinical trials. The vaccine—licensed by Pfizer—targets a mutation on the epidermal growth factor receptor. In one study, the vaccine more than doubled the survival time in patients with glioblastoma. John Sampson, MD of Duke University, who presented the data at the American Society of Clinical Oncology was quoted as saying, “That is almost unheard of.” A second study, using a different design and dosing schedule, resulted in a median survival time of 26 months in the experimental arm compared with 15 months in patients receiving standard therapy. Although promising, Dr. Gilbert said that these results were “very preliminary.”

Future Directions

New approaches continue to be needed. Addressing the vascular nature of gliomas, investigators have demonstrated that the anti-angiogenic agent bevacizumab [Avastin; Genentech] alone or in combination with irinotecan can produce robust responses as salvage therapy.

The vascular endothelial growth factor (VEGF) receptor can also be targeted successfully with

cediranib [Recentin; AstraZeneca], an oral pan-VEGF receptor tyrosine kinase inhibitor. Cediranib given daily cut tumor volume by 50% in patients with recurrent tumors, and prolonged survival to 10 months in half the patients in a Phase 2 trial.

LIVER CANCER: COMPLEMENTARY PHASE 3 RESULTS

For the GI Cancers Highlights, a study on sorafenib [Nexavar; Onyx Pharmaceuticals] in Asians with liver cancer was the only liver cancer study noted by Margaret Tempero, MD, of the University of California, San Francisco. The Phase 3 study of 226 Asian patients with advanced liver cancer (largely related to hepatitis B) found a doubling in time to progression and disease control rate over placebo. Sorafenib [Nexavar; Onyx Pharmaceuticals/Bayer Healthcare] demonstrated clear benefit that was comparable with results from the previous SHARP trial, despite poorer health status and more metastases among the Asian subjects, reported Ann-Lii Chen, MD, of National Taiwan University Hospital, Taipei.

“Any doubts about whether sorafenib would be effective in the hepatitis B subset have been laid to rest,” commented Dr. Tempero.

GI cancer expert Jordan Berlin, MD, of Vanderbilt, added that these findings were the “key data” on liver cancer presented at the meeting. “It’s nice to see that the Chinese data backs up data from the SHARP trial, and it says that sorafenib probably works across a variety of forms of hepatocellular cancer,” he told OBR.

Sorafenib is now being evaluated in non small-cell lung cancer. A Phase 2 study by Schiller et al was noted by Georgio Scagliotti, MD, of the University of Torino, Italy, who presented the Lung Cancer Highlights. As a single agent, sorafenib was associated with a doubling in disease control rate and progression-free survival and a trend toward improved overall survival in heavily pretreated patients with advanced cancer. “Most findings with other targeted agents have been negative,” noted Dr. Scagliotti.