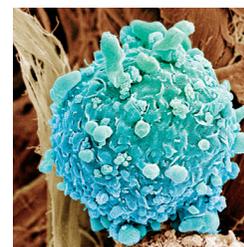


Second European Post-Chicago Melanoma Meeting 2012

Walter Alexander



After the immunotherapeutic agent ipilimumab (Yervoy) demonstrated a 4-month increase in the survival of patients with metastatic melanoma, it was approved in March 2011. That event ended a 13-year drought in FDA approvals for melanoma since the approval of interleukin-2 (IL-2, Proleukin) in 1998. Although IL-2 did extend survival, it is rarely used because of toxicity.

With interest piqued by new developments in melanoma therapy, 480 oncologists attended the inaugural European Post-Chicago Melanoma Meeting last year. This year's Second European Post-Chicago Melanoma meeting (June 21 and 22, 2012) similarly welcomed 481 specialists to reviews and analyses of research on CTLA-4 antibodies, selective kinase inhibitors, new vaccination approaches, and other innovative agents under development for intratumoral and systemic therapies.

Selected sessions on targeted and chemotherapeutic agents, immunotherapies, and the continuing role of chemotherapy are presented here.

Targeted and Chemotherapeutic Drugs

Dabrafenib, a *BRAF* Inhibitor

- Jean-Jacques Grob, MD, Professor of Dermatology, Hôpital Ste. Marguerite, Marseille, France

Mutations of the serine/threonine-protein kinase *BRAF* protein are found in 80% of melanomas. Vemurafenib (Zelboraf, Genentech/Daiichi Sankyo), a specific inhibitor of *BRAF*, was approved by the FDA for metastatic melanoma in August 2011.

Dabrafenib (GlaxoSmithKline, GSK 2118436), tested in the BREAK-2 trial, demonstrated a 59% confirmed response rate with a median progression-free survival (PFS) of 6.3 months. Like vemurafenib, it showed activity against *V600E* and *V600K* *BRAF* mutations.¹

BREAK-3 was a phase 3 randomized, open-label study comparing dabrafenib (150 mg twice daily) with dacarbazine for injection (DTIC, Dome/Bayer) (1,000 mg/m² intravenously every 3 weeks) in 250 previously untreated subjects with *BRAF*-mutated, metastatic stage III/IV melanoma. The primary endpoint of investigator-assessed PFS was a median of 6.7 months for dabrafenib and 2.9 months for dacarbazine. The benefit, Dr. Grob commented, was similar to that found for vemurafenib when compared with dacarbazine.

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The PFS hazard ratios (HRs) for dabrafenib ranged from 0.23 to 0.38 for Eastern Cooperative Oncology Group (ECOG) status, lactate dehydrogenase (LDH) level, age, sex, and disease stage subgroups.

Adverse effects were similar to those with vemurafenib, but pyrexia was more common and hyperkeratosis and photosensitivity were less common (3%). Dose modifications (3%), reductions (18%), and interruptions or delays (27%) were needed at identical rates for dabrafenib and dacarbazine.

In a phase 2 study (BREAK-MB) among treatment-naïve patients (n = 172) with *BRAF V600E/V600K* brain metastases receiving dabrafenib 150 mg twice daily, disease control (defined as complete response + partial response + stable disease) was achieved in similar proportions of patients with and without prior brain treatment (81%/89%, respectively, for *V600E* and 33%/50%, respectively, for *V600K*).

In the *V600E* group, PFS was roughly 16 months and median overall survival was about 32 months, with or without prior brain treatment. Results in the *V600K* groups were also positive but less dramatic than in the *V600E* subjects.

"These unprecedented response rates and survival may completely change our approach to brain metastases in *BRAF*-mutated patients," Dr. Grob said.

A further study of dabrafenib in melanoma (phase 1/2), in combination with the oral *MEK1* and *MEK2* (MAP kinase kinase) inhibitor trametinib (GlaxoSmithKline, GSK 1120212), revealed a highly encouraging PFS of 10.8 months for patients receiving dabrafenib/trametinib (150 mg twice daily/2 mg once daily). The clinical activity with the combination, Dr. Grob said, was clearly better than with the *MEK* inhibitor alone.

"Dabrafenib is a real competitor for vemurafenib with a slightly different toxicity profile," he concluded.

Trametinib in Advanced Melanoma

- Dirk Schadendorf, MD, Professor of Dermatology and Director, Department of Dermatology, University Hospital Essen, Essen, Germany

Among the more than 10 mitogen-activated ERK kinase (*MEK*) inhibitors in clinical development, Dr. Schadendorf said, trametinib (GSK 1120212), a highly selective allosteric inhibitor of *MEK1* and *MEK2*, has the most favorable features, including constant target inhibition via a half-life beyond 24 hours and a minimal potential for peak concentration-driven toxicities.

In the METRIC phase 3 melanoma study, 322 patients with the *V600E* or *V600K* mutation received trametinib; 214 patients received 2 mg once daily, and 108 patients received chemotherapy with dacarbazine (DTIC) or solvent-based paclitaxel (Taxol, Bristol-Myers Squibb). For the primary endpoint of PFS in patients with *BRAF V600E* melanoma, the median PFS was 4.8 months with trametinib and 1.4 months with chemotherapy.

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“The hazard ratio was a dramatic 0.44 for trametinib ($P < 0.001$),” Dr. Schadendorf said.

Most patients experienced tumor shrinkage or at least disease stabilization, and the PFS benefit was seen for all subgroups, irrespective of mutation status, age, sex, disease stage, or lactate dehydrogenase (LDH) levels. An overall survival benefit was achieved in 54% of the patients even though 47% of chemotherapy patients were switched to trametinib.

Trametinib toxicities were manageable, tolerable, and reversible, Dr. Schadendorf said, with rash (57%), peripheral edema (26%), and fatigue (26%) being the most common events. There were no reports of squamous cell carcinoma or hyperproliferative skin lesions.

Dr. Schadendorf also reviewed an efficacy and safety trial of a small-molecule *MEK* inhibitor, MEK162 (Array BioPharma/Novartis). Enrolled patients had locally advanced and unresectable or metastatic cutaneous melanoma with the *BRAF V600* mutation ($n = 35$) or the neuroblastoma *RAS* viral (*v-ras*) oncogene homolog (*NRAS*) mutation ($n = 28$). Median PFS was similar for both *NRAS* (3.65 months) and *BRAF* (3.55 months) mutations.

Dr. Schadendorf noted that although overall response rates were a little lower than with *BRAF* inhibitors, stabilization rates were higher with trametinib.

“I think combinations will be the way to go,” he stated.

Immunotherapies

Ipilimumab (Yervoy)

- Michael Maio, MD, Professor of Oncology, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy

Three-year results from the study comparing ipilimumab (Yervoy, Bristol-Myers Squibb) plus dacarbazine (DTIC) with placebo plus dacarbazine in 502 patients revealed overall survival rates of 20.8% for the ipilimumab combination and 12.2% for the placebo/dacarbazine combination. In the company's expanded access program for ipilimumab 10 mg/kg, 17% of patients (138/812) were alive after 3 years. Across a range of studies with ipilimumab 10 mg/kg, overall survival rates ranged from 20.4% to 25.4%.

In Dr. Maio's review of an ongoing phase 2 study of a first-line combination of ipilimumab and temozolomide (Temodar, Schering/Merck) in 64 patients with metastatic melanoma,² the overall response rate was 28% with a median PFS of 5.1 months. Median overall survival has not been reached.

A phase 2 multicenter trial in patients with metastatic melanoma, the M1 Italian Network for Tumor Biotherapy trial (NIBIT-M1) combined ipilimumab with fotemustine (e.g., Muphoran, Servier), an agent widely used in Europe that crosses the blood-brain barrier.³ Among 20 patients with brain lesions, the 1-year PFS rate was 45% and the 1-year survival rate was 54.2%. Median overall survival has not been reached. It seems, Dr. Maio said, that regardless of prior radiotherapy, the combination of ipilimumab and fotemustine can also be effective in this population.

“I personally think we can achieve a lot with ipilimumab, but we do have to improve its activity with different combinations of therapy,” he concluded.

Talimogene Laherparepvec (T-VEC):

Clinical Overview

- Dirk Schadendorf, MD, Professor of Dermatology, and Director, Department of Dermatology, University Hospital Essen, Essen, Germany

Tumor-targeted oncolytic viruses, said Dr. Schadendorf, have the potential for greater potency and selectivity than other melanoma treatments. Their property of direct replication and amplification in tumor tissue produces direct lysis, the expression of toxic proteins, and an enhanced immune response.

Amgen's T-VEC (formerly, Oncovex^{GM-CSF}) is an oncolytic herpes simplex virus type-1 strain engineered to replicate selectively in tumor cells and to express granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF recruits dendritic cells to tumor sites, and the dendritic cells process and present tumor-specific antigens to mediate a tumor-specific immune response.

In phase 2 results among 50 patients with stage IIIc or stage IV melanoma and injection-accessible tumors (74% had been previously treated), the response rate after a median follow-up of 18 months was 26% (16% complete responses and 24% durable responses of more than 6 months). Patients had received T-VEC injections every 2 weeks for eight cycles, with 16 additional cycles if they experienced an inflammatory reaction, a partial response, or stable disease. The 1-year survival rate was 58%, and the 2-year survival rate was 52%. Two additional complete responses were reported after surgery, and three complete responses were further reported during an extension period.

T-VEC was “quite safe,” Dr. Schadendorf said, with little grade 3 toxicity (8% of patients reported fatigue, and 6% reported asthenia).

Dr. Schadendorf noted that the best responses were found in patients with lower tumor loads and normal levels of lactate dehydrogenase (LDH). Inflammation and regression of tumors beyond the injection site (including noncutaneous liver metastases) after 4 months of treatment seemed to indicate a systemic immunologic response.

Enrollment in the phase 3 Oncovex Pivotal Trial in Melanoma (OPTiM) is completed ($n = 430$).⁴ In this trial, patients have unresectable stage IIIb, IIIc, or IV melanoma. Results are expected to be available in 2013.

In response to the questions about the potential role of T-VEC, Dr. Schadendorf said, “I think targeted agents clearly have an effect but are not curing any patients. So agents like T-VEC that amplify and maintain immunologic responses could be a good partner, for example, with ipilimumab or anti-PD-1 agents.”

The programmed death-1 (PD-1) pathway has emerged as an important tumor-evasion mechanism.⁵

Intralesional Rose Bengal (PV-10)

- Sanjiv S. Agarwala, MD, Professor of Medicine, Temple University School of Medicine, Philadelphia, Pa.; and Chief, Oncology & Hematology, St. Luke's Cancer Center, Bethlehem, Pa.
- Vernon K. Sondak, MD, Chair, Department of Cutaneous Oncology, H. Lee Moffit Cancer Center, Tampa, Fla.

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Is Chemotherapy Still an Option?

The Continuing Role of Chemotherapy

- Sanjiv S. Agarwala, MD, Professor of Medicine, Temple University School of Medicine, Philadelphia, Pa.; and Chief, Oncology & Hematology, St. Luke's Cancer Center, Bethlehem, Pa.

Dr. Agarwala opened by saying that when he was assigned to take on the challenging topic of whether or not chemotherapeutic agents still have a role, in light of the array of new impressive therapies, he was tempted to simply answer it with a “no” and leave. But on thinking about it, he saw it as a serious issue and decided to offer some data and some “philosophy.”

In the U.S., about 76,250 new cases of melanoma with 9,180 deaths are expected in 2012. The incidence is increasing, but mortality curves are steady at more than 10% and are roughly identical with rates for stage IV disease.

Noting the available treatments—chemotherapy (single-agent or combination); immunotherapy (single-agent or biochemotherapy); and targeted (personalized) therapy—Dr. Agarwala said, “Some of these survival-prolonging therapies, which do so only modestly, may not really move this curve.”

Response rates for single-agent chemotherapy with dacarbazine (DTIC), carmustine (BiCNU, Bristol-Myers Squibb), lomustine (CeeNu, Bristol-Myers Squibb), cisplatin (Platinol), vincristine, vinblastine, paclitaxel (Taxol), and temozolomide (Temodar) have ranged from 12% to 23%. For example, the 1-year survival rate with the standard agent, dacarbazine, has averaged 27% across trials, with a 13% response rate.

Long-term remissions with dacarbazine are rare, and this agent has never been tested against best supportive care. The efficacy of temozolomide, which is widely used to treat brain cancers but is not approved for melanoma, has been roughly equivalent to that of dacarbazine.

When the once-widely administered “Dartmouth” combination chemotherapy regimen (dacarbazine, cisplatin, carmustine, tamoxifen) was tested against carboplatin/paclitaxel, no benefit was apparent.⁶ Also, when sorafenib (Nexavar, Bayer/Onyx) plus a combination of carboplatin (Paraplatin, Bristol-Myers Squibb) and paclitaxel (Taxol) was tested against placebo plus carboplatin/paclitaxel, progression-free survival was identical (HR = 0.906, $P = 0.492$).⁷ The study was conducted in patients whose disease had progressed with a regimen containing dacarbazine or temozolomide.

Other trials of chemotherapy combinations also showed no survival advantage over dacarbazine alone.

Dr. Agarwala said, “This has convincingly shown us that combining chemotherapy drugs is not better than single-agent chemotherapy, but it adds toxicity, perhaps with some higher response rates but without improved survival.”

Various combinations of chemotherapy agents “with some immunotherapy thrown in,” when evaluated in randomized trials against chemotherapy, also showed no advantage.

“If you give something that doesn't work, it doesn't matter how much you give or how often you give it,” Dr. Agarwala commented.

However, the recent presentation of data at the 2012

PV-10 is a sterile, non-pyrogenic solution of Rose Bengal disodium (10% RB) for intralesional injection. It has an established safety history in prior diagnostic and ophthalmic use. PV-10 is not metabolized; it has a short circulatory half-life of about 20 minutes. PV-10 is excreted via bile. It accumulates selectively in the lysosomes of cancer cells and elicits autolysis within 30 to 60 minutes.

Dr. Agarwala's seven-center phase 2 trial in the U.S. and Australia enrolled 80 patients with stage III/IV melanoma. The median age of the patients was 70.0 years, and 61% were men. In this study, which was completed in June 2012, investigators treated up to 10 target lesions and observed one or two untreated bystander lesions. Re-treatment of new or partially responsive lesions was allowed as necessary.

Subjects received from one to four treatments (median, two treatments). The median dose was 1.6 mL, and the median cumulative dose was 3.4 mL. Adverse events were predominantly locoregional and mild to moderate. No grade 4 or 5 events were reported, but there were seven reports of grade 3 injection-site pain.

The objective response rate (defined as complete response + partial response) was 58% in target lesions and 40% in bystander lesions. Locoregional disease control (defined as the addition of stable disease to complete and partial responses) was reported for 80% of the target lesions and for 60% of the bystander lesions. Bystander effects in untreated lesions correlated closely with responses in injected lesions. A systemic response was defined as stasis or regression of distant visceral lesions in several patients.

The new analysis reported by Dr. Agarwala focused on responses of target lesions stratified according to disease stage. Stage III melanoma subjects exhibited consistently robust responses to PV-10. Furthermore, responses were significantly more durable in stage III patients (mean, 9.6+ months) compared with 3.1 months for stage IV melanoma patients ($P < 0.001$).

Response rates in stage IV patients were adversely affected by greater target tumor burden at baseline and by the progression of non-study lesions that precluded repeated treatment.

Dr. Agarwala noted that the planned phase 3 trial of PV-10 will include about 180 subjects with stage IIIb and IIIc disease.

In an interview, Dr. Sondak noted that locally or regionally advanced tumors without metastatic disease can be a severe problem for patients and for surgeons.

“The logical approach is a localized one,” he said.

However, whereas radiation would be the obvious solution for many cancers, melanoma is notoriously poorly responsive to this treatment. Fortunately, Dr. Sondak said, a number of tools have come along to treat this group of patients; some—like V-TEK (Oncovex^{GM-CSF}) and PV-10—create an immune effect.

He said further, “If it's shown that they are causing local destruction of tumors and are causing T-cell infiltrates, I'm interested in seeing how I can take advantage of that. If phase 3 trials confirm their benefits, adding systemic immunological therapies like ipilimumab and PD-1 with intralesional injection therapies would be an extremely logical combination.”

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American Society of Oncology (ASCO) meeting by Lawrence Flaherty, MD, of Wayne State University in Detroit, Mich., did show a relapse-free survival benefit for a short course of biochemotherapy (cisplatin, vinblastine, dacarbazine, interleukin-2 [aldesleukin, Proleukin, Prometheus], and interferon) versus high-dose interferon in the adjuvant setting, without a survival advantage and with higher grade 4 toxicity.⁸

Ipilimumab (Yervoy) and vemurafenib (Zelboraf) have broken the “survival barrier.” Ipilimumab/dacarbazine was superior to placebo/dacarbazine, with a respectable 10.3% response rate and an overall survival of 9.1 months.⁹

In a 2012 ASCO presentation of a *post hoc* analysis, vemurafenib showed an overall survival advantage over dacarbazine (13.6 months, HR = 0.70, $P < 0.001$).

“The treatment landscape has changed,” Dr. Agarwala said. He offered an algorithm for current treatment outside of clinical trials (Table 1).

Finally, he noted that 75% of the world’s population of 6.84 billion people live outside of North America, Europe, and Australia.

Dr. Agarwala said, “In absolute numbers, there are probably more non-Caucasians with melanoma than Caucasians, which means that less than a third of melanoma patients live in nations with access to new therapies.”

The hard facts, he continued, suggest that even that with new survival-prolonging therapies, most patients do not respond, and most patients who do respond ultimately experience disease progression and are not cured.

The cost of dacarbazine, he said, is about \$226.89 per month; vemurafenib costs \$9,400 per month, and ipilimumab costs \$30,000 per cycle.

“What will a *BRAF/MEK* combination cost? We are not even going to go there,” he commented.

Dr. Agarwala concluded, “For more than 50% of metastatic melanoma patients worldwide, outside of clinical trials, chemotherapy is not an ‘option’; it is the only option.”

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Table 1 Melanoma Treatment Algorithm, 2012

Setting		Phase 3 Evidence	Alternative
1st-line therapy	<i>B-raf</i> -mutated	Vemurafenib Ipilimumab	High-dose IL-2 Chemotherapy
	<i>B-raf</i> wild-type	Ipilimumab	High-dose IL-2 Chemotherapy
2nd-line therapy	<i>B-raf</i> wild-type Ipilimumab failure	Chemotherapy	?
	<i>B-raf</i> -mutated Vemurafenib failure	Ipilimumab, chemotherapy	

IL = interleukin.
Adapted with permission from Sanjiv S. Agarwala, MD.