

ASCO '10

» Innovative Advancements in Treating Cancer: Beyond Targeted Therapies

By Corey Pelletier and Richard Wagner

Consistent with the theme of “Advancing Quality Through Innovation” at this year’s American Society of Clinical Oncology’s (ASCO) 46th Annual Meeting, held in Chicago, Illinois, were the many presentations representative of novel and inventive approaches to cancer therapy. As evidenced by the over 4,500 presentations, innovation has many guises and goes beyond targeted therapies to include new product classes, novel patient segments, new treatment practices, and inventive devices or methods of drug delivery—all of which ultimately have the potential to advance cancer care and deliver progress.

In examining these many guises of innovation, some of the greatest leaps forward in cancer treatment have come when predictive biomarkers of treatment efficacy and associated targeted therapies have enabled patients to receive personalized therapies. For instance at last year’s ASCO, the big story was epidermal growth factor receptor (EGFR) mutation in patients with non-small cell lung cancer (NSCLC)—with two trials showing an impressive progression free survival (PFS) benefit and low toxicity when biomarker-defined patients were treated with Iressa [gefitinib; AstraZeneca].

At this year’s meeting, the EML4-ALK fusion gene emerged as the newest molecular marker for patients with NSCLC. Paired with crizotinib (Pfizer)—the leading ALK inhibitor in development—interim results of a Phase 1/2 trial in ALK-positive NSCLC patients were presented. In this cohort, crizotinib produced an objective response in 57% of patients with an impressive disease control rate of 87%. Moreover, investigators estimated a 72% probability of treated patients being progression free at 6 months after starting their therapy. This is a remarkable result considering that with best available chemotherapy half the patients would have progressed in 3 months or less.

The EML4-ALK fusion is rare, present in only about 5% of the NSCLC population overall. This low incidence seemingly presents a commercial obstacle, i.e. will it be financially viable to develop a drug specifically for this niche population? Still, it is important to remember that due to the large population of NSCLC, 5% translates into about 4,000 new patients in the United States each year. From that perspective, the EML4-ALK segment looks comparable to chronic myeloid leukemia, an indication revolutionized by the commercial success of Gleevec [imatinib; Novartis]. Like the EGFR mutation, the EML4-ALK fusion is associated with clinical features. Such features include adenocarcinoma histology and non-smoking status; presence of these features can help direct testing only to those patients with tumors that are most likely to harbor this mutation.

Adding to the excitement of a novel molecular marker for NSCLC, the study illustrates the rapidity with which discoveries may be translated to clinical benefit for patients. The EML4-ALK fusion protein was first reported in 2007; as more genetic subtypes are identified, NSCLC is changing from a cancer once simply characterized as “non small cell” to a collection of distinct cancers where treatment choice depends on characteristics of the tumor, such as histology or even which mutation is present in the molecular profile.

Advancements in Melanoma

For 30 years, survival for metastatic melanoma patients has not improved. Measured against that dismal history, the data presented on ipilimumab (Bristol-Myers Squibb) during a plenary session was unprecedented. Median overall survival (OS) in patients receiving ipilimumab (either alone or in combination with peptide vaccine) was approximately 10 months, compared with 6.4 months in patients receiving the pep-



Top 10 Media Stories from ASCO '10

With about 4,500 studies presented at this year's ASCO meeting, some of the stand-outs that have grabbed the attention of researchers, MDs, analysts/investors and the media alike include exciting data from hard to treat cancer types, such as melanoma, ovarian cancer, and CML. This year's theme of "Advancing Quality Through Innovation" proved to be a timely one, and built on the paradigm that is advancing personalization of cancer care, which, by the data presented here, took another giant step forward. Below, OBR presents, in no particular order, an overview of what were considered to be some of the most riveting studies presented at this year's meeting. We hope you agree.

tide vaccine alone. More impressive than the difference in median OS was an apparent plateau in the survival curve, suggesting 20% of patients treated with ipilimumab enjoy durable clinical benefit extending out to 4 years. Any survival plateau is rare in cancer; to speak of one in melanoma, where even incremental improvement has been elusive, is remarkable.

The immune-based mechanism of action for ipilimumab is particularly innovative, contrasting with more typical approaches to cancer immunotherapy. The compound is a fully human monoclonal antibody against CTLA-4, an antigen on T cells that down-regulates T-cell activation. By blocking CTLA-4 mediated immune suppression, ipilimumab releases the brakes on T-cell response, thereby stimulating the expansion of T-cell populations to attack the tumor.

The dominant vaccine paradigm thus far has been based on sequential vaccination with tumor-derived antigens to elicit an immune response, ideally causing tumor regression with minimal toxicity (in the case of Provenge [sipuleucel-T; Dendreon], antigen-presenting cells from the patient are primed with a tumor antigen). While vaccines such as Provenge may successfully stimulate the immune system against the tumor, the tumor may possibly blunt the attack by turning off the anti-tumor immune response, an unappreciated hallmark of cancer. Ipilimumab takes the converse strategy—by hindering the ability of the tumor to keep the immune system at bay, any dormant immune response can be unleashed, specific to the individual and tumor composition.

Clearly active, ipilimumab is nevertheless an agent to be used with care. Because it activates the immune system, ipilimumab has a unique toxicity profile whereby the immune system may attack the patient as well as the tumor. These autoimmune breakthrough events, such as dermatitis, enterocolitis, hepatitis, or endocrinopathies are significant and may potentially cause life-threatening complications that require early intervention, usually with high-dose steroid administration. Therefore, management of ipilimumab toxicity requires

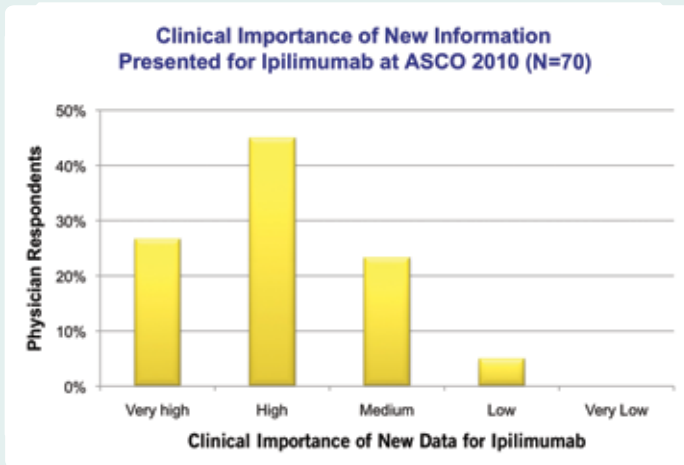
[cont. on pg 26 >>](#)

RANK	STORIES
01	For Bristol-Myers Squibb, ipilimumab, a human CTLA-4 mAb candidate, demonstrated significant improvement in overall survival in previously-treated advanced melanoma patients. In a Phase 3 study (n=676), patients receiving ipilimumab had a median survival of 10.1 months compared with a median overall survival of 6.4 months in patients treated with a gp100 peptide vaccine alone. According to Steven O'Day, MD, of The Angeles Clinic and Research Institute, Los Angeles, CA, who presented the trial results at ASCO, "For the first time, a significant improvement in overall survival has been demonstrated in previously-treated advanced melanoma patients in a large, randomized Phase 3 study." During the plenary session, he said that... "after 30 years of failed studies, there might finally be an option for patients..." Although side effects can be severe, investigators from the study report that most are reversible with appropriate treatment.
02	In two separate head-to-head trials, new data showed that Bristol-Myers Squibb's (BMS) Sprycel (dasatinib) and Novartis' Tassigna (nilotinib) both proved superior as therapies in newly diagnosed patients with chronic phase chronic myeloid leukemia (CML) compared with first-line, gold standard CML treatment—Gleevec [imatinib; Novartis]. In the BMS study (n=519), 77% of patients in the Sprycel-arm vs. 66% of patients in the Gleevec-arm achieved confirmed complete cytogenetic response (two consecutive assessments) by 12 months (P=.007). In the Tassigna study (n=846), 18-month median follow-up data showed three times more patients achieved undetectable disease at the molecular level with Tassigna than with Gleevec. Until June 17, both Sprycel and Tassigna were approved only as second-line therapies for patients with CML who either could not tolerate Gleevec or who had failed on the therapy—but on that date, U.S. regulators approved Tassigna as a front-line treatment on the basis of data from the Tassigna vs. Gleevec head-to-head trial. Which leaves us wondering: Can Sprycel be far behind?
03	Results from Roche's large, international, Phase 3 PRIMA study (n=1,217) showed that first-line maintenance use of MabThera (rituximab) plus chemotherapy doubled the likelihood of people with advanced follicular lymphoma living without their disease worsening. After 2 years of follow-up, study data showed that 82% of patients who received MabThera maintenance therapy were in remission compared with 66% of patients who did not receive the treatment (hazard ratio 0.50; P<.0001). MabThera is known as Rituxan in the United States, and has been cont. on pg 27 >>

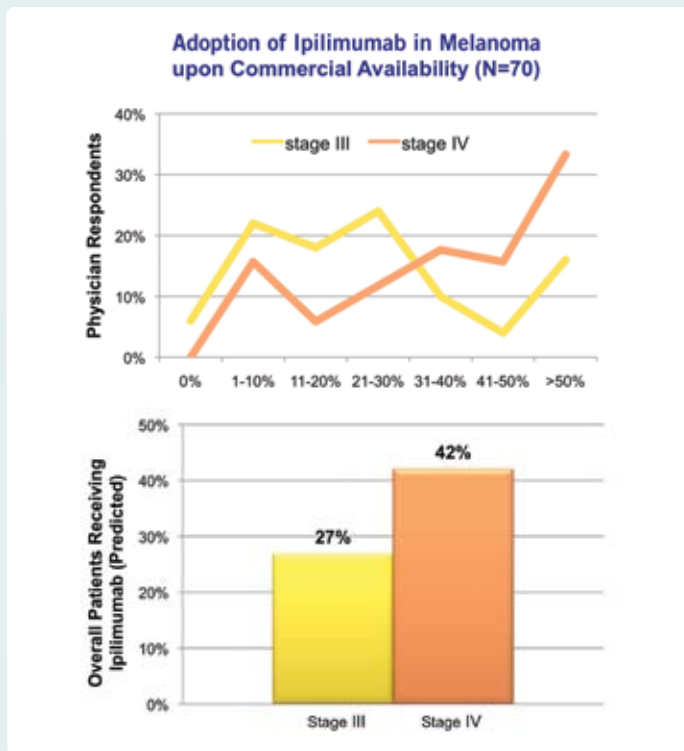
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» DID YOU KNOW?

Results from a post-ASCO hem/onc quick poll conducted by The Arcas Group revealed that physicians found new information presented on ipilimumab to be of high clinical importance.



The quick poll also revealed that physician response to new data presented at ASCO predicts strong market adoption of ipilimumab in stage III/IV melanoma patients.



Source: MDoutlook, powered by The Arcas Group. ASCO June 2010.

a multidisciplinary, experienced team that is able to recognize these toxicities where they occur. Until physicians become skilled at detecting and treating these toxicities and guidelines are established for proper use, ipilimumab may not reach its full potential.

Inspired by ipilimumab's example, interim results from another immune-stimulatory drug were also presented, though on a smaller stage and with less dramatic impact. MDX-1106 (Bristol-Myers Squibb) is a fully human antibody that blocks PD-1, another receptor capable of down-regulating T-cell activity. Although the data are early, the results presented on the Phase 1 dose escalation study in solid tumors were particularly exciting—of 46 metastatic melanoma patients, 15 had tumor shrinkage qualifying as a partial response and another 10 patients had disease stabilization. Not only did MDX-1106 display an impressive response rate, but the drug demonstrated acceptable tolerability at all dose levels tested, appearing to produce fewer immune-related adverse events than ipilimumab.

Devices Driving Innovation

Although drugs with novel targets or mechanisms of action typically garner the most attention, two innovative delivery technologies presented promising data. The more advanced technology, Delcath Systems' Percutaneous Hepatic Perfusion (PHP) delivery device, reported results from their ongoing randomized Phase 3 study administering melphalan [Alkeran; GSK] in metastatic melanoma patients with unresectable liver metastases. The PHP device employs a minimally invasive technique using a set of specific balloon-tipped catheters that enable high-dose chemotherapy to be administered in isolation to the liver. The chemotherapy-saturated blood is then filtered before it is returned to the patient's circulation. In this study, hepatic progression free survival (the primary endpoint) was 245 days in the PHP arm and 49 days in the best alternative care arm (supportive care, systemic or regional chemotherapy or chemo-embolization). Overall PFS was also longer at 189 vs. 46 days, respectively. No OS benefit



was observed despite these gains, possibly because 55% of the patients from the best alternative care arm crossed over to PHP upon progression.

If approved, this device will be the first that allows a noninvasive approach to isolated chemotherapy of hepatic metastases, a frequent site of disease spread but one where surgery can be difficult. In addition, patients with metastatic uveal (ocular) melanoma, a condition that is genetically distinct from the skin (cutaneous) form, were included in the study and enjoyed benefit. Since there are no approved or widely accepted treatments for metastatic ocular melanoma, approval of this device could meet an unmet need for a difficult to treat subpopulation. Finally, if the Delcath PHP device is a platform that can be used with different drugs, then the possibility exists for the local delivery of agents that may be more effective than melphalan.

Another promising technology described systemic delivery of small interfering RNA (siRNA), a key stepping stone to converting the promise of siRNA into real clinical therapies. This dose escalation trial in patients with solid refractory cancers was the first-in-human siRNA Phase 1 study of a targeted nanoparticle delivery system. The nanoparticles used consisted of a liposomal vehicle, a transferrin protein targeting ligand and siRNA against ribonucleotide reductase—the target of Gemzar [gemcitabine; Eli Lilly]. Although the efficacy observed was minimal (best response was one case of stable disease), the treatment regimen was generally well tolerated and resulted in knockdown of the target gene in patient biopsies, constituting proof of concept. For the first time, siRNA-based cancer therapeutics, which have the potential to target key oncogenic targets now considered undruggable like RAS, may be a realistic possibility.

Using Old Drugs in New Settings

A common challenge for oncologists is deciding how to optimally incorporate a new drug into existing practice, even after validation in a randomized trial. An innovative theme that emerged in multiple tumor types was the use of maintenance therapy to prevent relapse, rather than waiting to use the drug at relapse. [cont. on pg 28 >>](#)

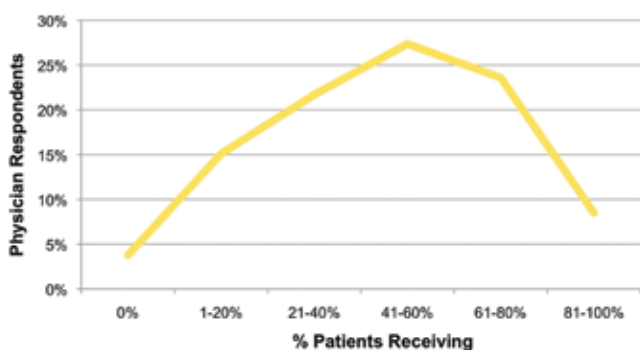
RANK	STORIES
03 (CONT.)	successfully administered both alone and in combination with standard chemotherapy regimens for patients whose follicular lymphoma has either recurred or has been resistant. What has not been studied up until now was the question whether rituximab maintenance therapy was beneficial in patients who have already received rituximab therapy during the induction phase. The PRIMA trial is a response to that question and establishes positive results of rituximab's use as maintenance therapy for patients with follicular lymphoma who have been initially treated with the drug.
04	Data from a Phase 3 study (n=1,873) from the Gynecologic Oncology Group (GOG) showed that adding Avastin [bevacizumab; Genentech] to initial chemotherapy treatment (paclitaxel and carboplatin) in women with previously untreated advanced ovarian cancer, and then administering Avastin as maintenance therapy for a total duration of up to 15 months, demonstrated a median progression free survival of 14.1 months compared with 10.3 months in women who received chemotherapy alone (hazard ratio=0.72; P<.0001). According to Robert Burger, MD, Director of the Women's Cancer Center at Fox Chase Cancer Center in Philadelphia, during a plenary session, "This translates into a 28% reduction in the risk of cancer progression or death." Although this is considered to be a well-powered and engineered study that included 3 treatment arms, questions remain regarding whether ovarian cancer is susceptible to bevacizumab, at what dose, and if the dose needs to be continuous.
05	In a head-to-head Phase 3 trial (n=1,901) which compared the efficacy and safety of Amgen's Prolia (denosumab) with Novartis' Zometa (zoledronic acid) in patients with hormone-refractory prostate cancer and bone metastases, data showed that denosumab is superior to zoledronic acid in significantly delaying the time to first on-study skeletal-related events (SRE) (hazard ratio 0.82; P=.008). The median time to first on-study SRE was 20.7 months for denosumab vs. 17.1 months for zoledronic acid. This study is the final of 3 pivotal trials involving over 5,700 advanced cancer patients that explored the potential of denosumab to treat bone metastases. These 3 studies form the basis of the clinical evidence package for denosumab in advanced cancer, and were submitted to regulatory authorities in the United States and the European Union. Denosumab specifically targets the RANK Ligand—the essential regulator of osteoclasts (the cells that break down bone)—and is the first and only FDA-approved RANK Ligand inhibitor. In June, the FDA approved the use of denosumab for the treatment of postmenopausal women with osteoporosis at high risk for fracture.
06	Exciting news was revealed from the EMBRACE study (n=762), in which significant median overall survival benefit for heavily pre-treated metastatic breast cancer patients was demonstrated. The new chemotherapy agent from Eisai, eribulin mesylate, is a nontaxane, microtubule dynamics inhibitor—a synthetic analog of halichondrin B, which is derived from a natural product isolated from sea sponges. The study is the first Phase 3 single agent study that met its primary endpoint of increased overall survival specific to this patient population, and may provide a new treatment option for these patients. Patients in the study cont. on pg 29 >>

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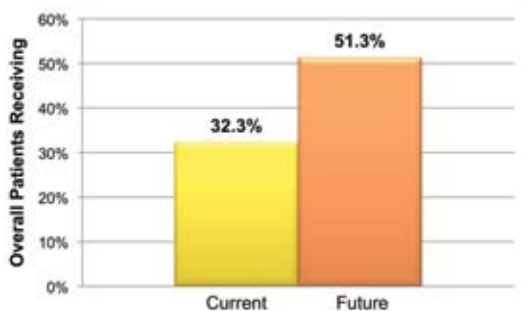
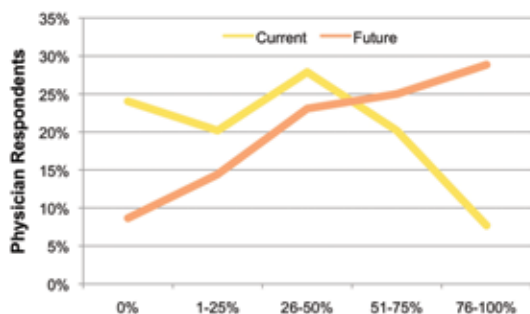
Results from a post-ASCO hem/onc quick poll conducted by The Arcas Group revealed that a majority of physicians use lenalidomide in >50% of patients with multiple myeloma (MM); nearly all oncologists use lenalidomide.

Total Current Use of Lenalidomide in Multiple Myeloma (N=120)



The quick poll also revealed that use of lenalidomide as maintenance therapy in MM is predicted to increase.

Change in Overall Use of Lenalidomide as Maintenance Therapy in Multiple Myeloma Following ASCO 2010* (n=120)



*Based on Abstracts 8017, 8018

Source: MDoutlook, powered by The Arcas Group. ASCO June 2010.

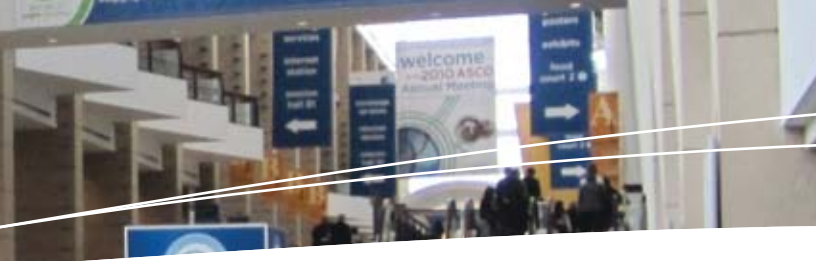
Two separate studies in multiple myeloma (MM), both exploring the efficacy of Revlimid [lenalidamide; Celgene] vs. placebo to delay PFS after autologous stem cell transplant, met their primary endpoints. A prolongation of PFS with Revlimid maintenance was observed regardless of stage, cytogenetics, and the type of induction therapy, suggesting benefit for all patients and in diverse approaches to transplant. Importantly, benefit was seen regardless of the level of response to initial therapy, distinguishing these results from those seen with a related drug, Thalomid [thalidomide; Celgene]. No survival benefit was seen, but given that strong association between relapse following transplant and death from MM, the PFS benefit will likely translate into a longer OS with further follow-up.

In another example, a Phase 3 randomized trial of Avastin [bevacizumab; Genentech] plus chemotherapy in newly diagnosed advanced ovarian cancer patients following surgery met its primary endpoint, demonstrating a 4-month prolongation of PFS when Avastin was combined with chemotherapy and followed by maintenance Avastin for 48 weeks. As with the MM trials, the ability of Avastin maintenance to increase OS has not yet been confirmed. But in this case, the linkage between PFS and OS is less clear.

When longer PFS does not mean patients live longer overall, is it clinically meaningful? If disease progression means appearance or worsening of disease-related symptoms, then quality of life may be improved. But in ovarian cancer, CA125 tests or routine scans often diagnose progressive disease while many patients remain asymptomatic. Until quality of life and final survival results are available, oncologists may move cautiously in adopting Avastin maintenance.

Concluding Thoughts

With the promise of even more impressive results for ipilimumab and further data to come from MDX-1106, these agents represent some of the most exciting in oncology today. However, it is important to remember that drugs are used because they improve outcomes, not because they represent clever approaches. A presentation of impact, although not necessarily reflecting a par-



ticularly innovative approach, was the randomized Phase 3 study of a novel taxane, Jevtana [cabazitaxel; sanofi-aventis] plus prednisone vs. mitoxantrone plus prednisone in second-line metastatic castrate-resistant prostate cancer. Jevtana plus prednisone increased survival by just over 2 months compared with mitoxantrone plus prednisone, the chemotherapy regimen physicians are using most in these patients. In June '10, Jevtana was approved by the FDA, to become the new standard of care. While another taxane may not look like innovation, patient outcomes are what matter most.

Other questions remain that are relevant across different tumor types. What is the optimal duration of maintenance therapy? Who needs maintenance and who does not? Where a clear PFS benefit has been observed, will maintenance also improve OS with longer follow-up? Is a benefit in OS necessary, or is PFS gain itself clinically meaningful? Although these questions need to be addressed, it is clear that the studies presented at this year's ASCO may change practice, shifting treatment goals from preventing, rather than treating, relapse. **CP RW**

About the Contributors of This Article

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RANK	STORIES
06 (CONT.)	who were randomized to receive eribulin survived a median of 2.5 months longer than patients who received Treatment of Physician's Choice (TPC)—defined as any approved single agent chemotherapy, hormonal treatment or biological therapy or palliative radiotherapy administered according to local practice—(overall survival of 13.12 months for eribulin vs. 10.65 months for TPC; $P=.04$). Chris Twelves, MD, lead investigator for the study and Professor of Clinical Cancer Pharmacology and Oncology from the University of Leeds and St. James's University Hospital, Leeds, United Kingdom, said, "These results show that eribulin significantly improved overall survival versus a variety of agents used in a real-world setting, which previously no single agent has shown."
07	Pfizer made a big impression with extremely positive Phase 1 study data ($n=82$) that showed at 8 weeks of treatment with its investigational drug, crizotinib—an ALK inhibitor in non-small cell lung cancer (NSCLC)—87% of patients with advanced NSCLC responded to treatment with 57% of patients showing tumor shrinkage. According to Yung-Jue Bang, MD, PhD, from Seoul National University College of Medicine in Korea, who presented the information, patient responses have been enduring (up to 15 months), and patients had a 72% probability of being progression free at 6 months. Crizotinib is a first-in-class compound that inhibits the tumor-specific protein ALK, and two upcoming Phase 3 studies will be enrolling ALK-positive patients—one study being a comparative trial with a pemetrexed-arm or a docetaxel-arm.
08	In surprising results, Eli Lilly and Bristol-Myers Squibb's Erbitux (cetuximab)—successful in treating metastatic colon cancer patients with the wild-type KRAS gene—failed to prolong survival for patients with early-stage colon cancer when added to standard treatments. After 16 months follow-up, patients with resected stage III colon cancer and wild-type KRAS were randomized to receive FOLFOX plus cetuximab ($n=955$) or FOLFOX alone ($n=909$). Three-years after starting treatment, 75% of patients treated with chemotherapy alone were alive without disease recurrence compared with 72% of patients treated with chemotherapy and Erbitux.
09	Excellent news on Delcath System's percutaneous hepatic perfusion (PHP) drug delivery system. In the PHP arm of the study ($n=44$), patients with hepatic metastases from ocular or cutaneous melanoma treated with melphalan (Alkeran, GlaxoSmithKline) showed median hepatic progression free survival of 245 days compared to 49 days in the Best Alternative Care (BAC) treatment arm ($n=49$). Median overall survival in the PHP arm was 298 days, compared with median overall survival of 124 days for those patients in the BAC arm that did not crossover. Although these data are extremely positive, limitations of the study were noted including it was not identified which patients had metastases only to the liver and which had metastases to other sites.
10	In the first, definitive Phase 3 study ($n=331$) to show results for patients with advanced medullary thyroid cancer (MTC), AstraZeneca's vandetanib significantly extended progression free survival, demonstrating a 54% reduction in the rate of progression compared with placebo. Currently, patients with advanced MTC have few or no options for treatment at this stage, and AstraZeneca plans to file regulatory submissions for approval with the FDA and the EMA this year. ORR