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CLINICAL INVESTIGATION

NEWS

Highlights from the American Society of Clinical Oncology 2011 Annual Meeting

'A time for hope' – new metastatic melanoma agent astounds at the ASCO

It has been announced that targeted therapy using vemurafenib has dramatically improved progression-free survival (PFS) and overall survival (OS) in patients with advanced melanoma with no previous treatment, compared with standard chemotherapy.

Advanced melanoma is currently one of the deadliest forms of cancer and melanoma incidence has climbed faster than any other cancer type over the past three decades. Vemurafenib targets V600E mutations in the *BRAF* gene, a mutation that effects an estimated 40–60% of melanoma patients.

The trial, known as BRIM-3, which demonstrates the effect of vermurafenib on advanced melanoma has been published online in the *New England Journal of Medicine,* to coincide with the presentation at the ASCO 2011 Annual Meeting.

It is an ongoing 675-patient Phase III study. The results demonstrated that at 6 months, OS was estimated at 84% (95% CI: 78–89) in the vemurafenib group and 64% (95% CI: 56–73) in the dacarbazine group. There is currently no median OS in the study owing to the lack of maturity in the data, explained Paul Chapman, Memorial Sloan-Kettering Cancer Centre, UK.

> "...the availability of vemurafenib is a major defining moment that will have an important effect on survival and quality of life"

Although the trial is ongoing, the PFS findings are final. Results demonstrated that patients receiving vemurafenib had a reduction in the risk for progression (or death) of 74% compared with patients receiving dacarbazine chemotherapy (hazard ratio: 0.26; $p < 0.001$). Mean PFS was 5.3 months in the vemurafenib group and 1.6 months in the dacarbazine group. Chapman stated that "it's unprecedented to report a trial this early" and explained that the PFS data constituted "an unprecedented level of difference".

A planned interim analysis for OS demonstrated that patients receiving vemurafenib had a reduction in risk for death of 63% (hazard ratio: 0.37; $p < 0.001$). Response rates were 48% for vemurafenib and 5% for dacarbazine ($p < 0.001$). The median follow-up for the interim analysis was 3.8 and 2.3 months in the vemurafenib group and dacarbazine group, respectively. An independent data and safety monitoring board reviewed the interim analysis and recommended that patients receiving dacarbazine cross over to vemurafenib.

The study has been positively embraced by many leading experts. Lynn Schuchter, from the Abramson Cancer Center at the University of Pennsylvania, PL, USA, and moderator of the press conference, stated that the study was "practice changing". She noted that responses with the new oral therapy can be dramatic and that within 72 h of treatment patients can show improvement.

The study has brought great hope, since this now means that in the past year two agents, vemurafenib and ipilimumab (which is approved by the US FDA), have emerged as effective treatments for metastatic melanoma. In an editorial that accompanies the published study, Marc Ernstoff, from the Dartmouth

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Combination of chemotherapy and immunotherapy improves overall survival in metastatic melanoma

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Medical School and Norris Cotton Cancer Center in Lebanon, NH, USA, wrote "the results of the BRIM-3 study represent a major shift in the way we think about and treat melanoma". He continued, "the availability of vemurafenib is a major defining moment that will have an important effect on survival and quality of life."

However, Ernstoff also highlighted some notes of caution. He stated that "the final estimate of survival outcomes is still to be determined" and that the complete response rate in the study was low, with two of the 219 patients (0.9%) receiving vemurafenib, having their tumor response evaluated. "The results of the final analysis will be necessary for the true reduction in risk of death" commented Kari Kendra, from Ohio State University in Columbus, USA. She pointed out that this is an "interim analysis, with 66% of the vemurafenib and 25% of the dacarbazine patients still undergoing treatment."

> "The results of the final analysis will be necessary for the true reduction in risk of death"

In addition to this study, a Phase I study presented at the ASCO indicated that combining two oral targeted therapies, the MEK inhibitor GSK212 and the BRAF inhibitor GSK436, had a good safety profile and preliminary antitumor activity in patients with advanced melanoma. This is a "time for celebration for our patients," said Schuchter, "a time for hope."

Sources: Chapman PB, Hauschild A, Robert C *et al*. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N. Engl. J. Med.* 364(26), 2507–2516 (2011); Ernstoff MS. Been there, not done that – melanoma in the age of molecular therapy. *N. Engl. J. Med.* 364(26), 2547–2548 (2011); 'Time to celebrate'; new metastatic melanoma agent wows ASCO: www.medscape.com/viewarticle/744013

A Phase III, randomized study, demonstrated improved overall survival (OS) in patients with previously untreated metastatic melanoma when first-line treatment was a combination of the immunotherapy drug ipilimumab (Yervoy™) and the standard chemotherapy drug dacarbazine (DTIC). This is the first time that a randomized trial for metastatic melanoma has followed patients for this long, therefore the results are the first to demonstrate the durability of the survival benefit.

Advanced melanoma is currently one of the deadliest forms of cancer and melanoma incidence has climbed faster than any other cancer type over the past three decades. Ipilimumab is a monoclonal antibody, which represents a new class of drug that activates the immune system's T cells, seeking and destroying melanoma cells.

This study, presented at the American Society of Clinical Oncology (ASCO) 2011 Annual Meeting, is the first to demonstrate that it is safe and effective for patients with advanced melanoma to combine chemotherapy and immunotherapy. The study included 502 patients with metastatic melanoma, including 250 who were randomized to ipilimumab plus dacarbazine and 252 who received placebo and dacarbazine.

After one year, the OS rate for the combination was 47.3% and 36.3% for DTIC alone. After two years, the OS rate was 28.5 % for the combination and 17.9% for DTIC alone. At three years, an OS rate of 20.8% was observed for the combination, that for DTIC alone was 12.2%. "This trial's three-year end point is significant" stated Jedd Wolchok, director of immunotherapy clinical trials and associate attending physician at Memorial Sloan-Kettering Cancer Center.

The safety profile of the combination of ipilimumab and dacarbazine was good, with no gastrointestinal perforations and a rate of colitis much lower than expected, based upon prior studies with ipilimumab alone. However, in the ipilimumab–DTIC group approximately 56% of patients compared to 27% in the DTIC-only group, had significant grade 3/4 adverse events from therapy, which included elevated liver enzymes.

Wolchok stated that future plans for research are to investigate combinations of different therapies with ipilimumab and to test other combinations of targeted agents and immune-modifying agents together as well.

Sources: Wolchok JD, Thomas L, Bondarenko IN *et al*. Phase 3 randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) vs DTIC alone as first line treatment in patients with unresectable stage III or IV melanoma. J. Clin. Oncol. 29(Suppl.) Abstr. LBA5 (2011); ASCO 2011: first-line ipilimumab plus chemo improves overall survival in metastatic melanoma: www.ecancermedicalscience.com/news-insider-news.asp?itemId=1799

Imatinib for 3 years could become the new standard of care for high-risk gastrointestinal stromal tumors

Results presented at ASCO 2011 Annual Meeting, from a prospective, randomized, multicenter, Phase III trial, have demonstrated that 3 years of treatment with imatinib (Gleevec®), compared with 1 year of treatment, improved overall and recurrence-free survival in patients with high-risk gastrointestinal stromal tumors (GISTs). It has been suggested that for those patients who are at risk for relapse, these findings could results in a 3-year course of therapy becoming the new standard of care.

The study consisted of 400 patients with GIST, a type of soft-tissue sarcoma that usually begins in the intestine or stomach. Patients in the study were at high risk for recurrence and after surgery were randomized to either 1 or 3 years of imatinib. Imatinib targets the abnormal proteins encoded by mutated *KIT* and *PDGFR*-α genes, found in approximately 90% of GISTs. Investigators found that 5-year recurrence-free survival was higher in the 3-year group (65.6%) compared with patients treated for 1 year (47.9%) after a median follow-up time of 54 months. In addition, for the 3-year group the 5-year overall survival was higher (92%) compared with patients for the 1-year group (81.7%).

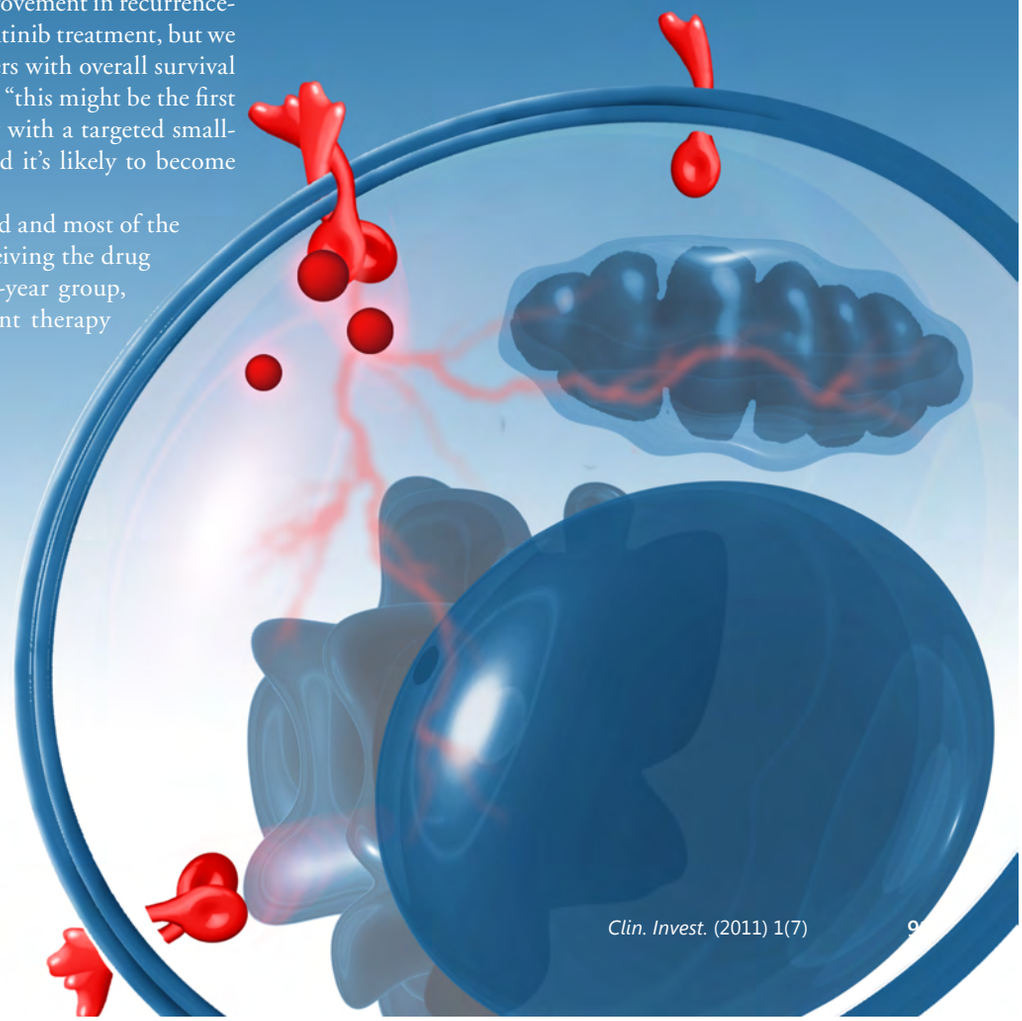
Heikki Joensuu, lead author of the study and professor of oncology at Helsinki University Central Hospital, Finland, said that "earlier studies have shown an improvement in recurrence-free survival with 1 year of adjuvant imatinib treatment, but we were surprised to also see better numbers with overall survival after 3 years of therapy". He added that "this might be the first example of long-term adjuvant therapy with a targeted small-molecule tyrosine kinase inhibitor, and it's likely to become standard treatment".

Generally, imatinib was well tolerated and most of the side effects were typical of patients receiving the drug on a shorter term. However, in the 1-year group, 7.7% who received 3 years of adjuvant therapy halted treatment because of adverse events, compared to 13.7% in the 3-year group. The need for continued monitoring and new research was stressed by Joensuu.

> "...this might be the first example of long-term adjuvant therapy with a targeted small-molecule tyrosine kinase inhibitor, and it's likely to become standard treatment."

Looking ahead, current studies are being conducted in analyzing GIST risk factors and looking at longer treatment times with adjuvant imatinib. This includes a single-arm, non-randomized study examining 5-year adjuvant treatment, which is currently underway.

Sources: Joensuu H, Eriksson M, Hatrmann J *et al.* Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO). *J. Clin. Oncol.* 29, Abstr. LBA1 (2011); ASCO 2011: three years of imatinib improves survival for high-risk gastrointestinal stromal tumours: www.ecancermedicalscience.com/news-insider-news.asp?itemId=1803



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Joanne Walker,
Commissioning Editor,
Clinical Investigation
Tel.: +44 (0)20 8371 6090;
E-mail: j.walker@future-science.com

Phase II results of ganetespib in advanced non-small-cell lung cancer

On Saturday 4th June 2011, Dr Geoffrey Shapiro, MD, PhD, from Dana-Farber Cancer Institute (MA, USA) presented exciting new Phase II data on the use of ganetespib in the treatment of advanced non-small-cell lung cancer (NSCLC). Ganetespib has been found to show promising clinical activity in patients with progressive disease.

Ganetespib is a potent inhibitor of Hsp90, a molecular chaperone required for the proper folding and activation of many cancer-promoting proteins. Hsp90 is recognized as a key facilitator of cancer cell growth and survival.

In the current Phae II trial, patients were enrolled who had advanced metastatic disease (stage IIIB and IV) who had failed prior therapy. These patients were then genetically profiled and divided into cohorts:

- EGFR mutation – cohort A (16 patients)
- KRAS mutation – cohort B (17 patients)
- Neither EGFR nor KRAS mutation – cohort C (25 patients)
- Adenocarcinoma only, also without EGFR or KRAS mutation – cohort D (37 patients)

The patients received ganetespib as a monotherapy once-weekly for 3 weeks of a 4-week cycle at a dose of 200 mg/m2. The primary end point of the study was progression-free survival (PFS) at 16 weeks. Secondary end points included objective response rate (ORR), disease control rate (DCR) at 8 and 16 weeks, PFS, overall survival, time to treatment failure, and safety and tolerability.

At the time of analysis, 76 patients were able to be evaluated, having received at least one dose of ganetespib and one follow-up scan:

- 14 in cohort A – of this group, five patients (36%) experienced tumor shrinkage. The stable disease rate at 8 weeks per RECIST was 7/14 (50%). The overall disease control rate was 50%.
- 13 in cohort B – of this group, eight patients (62%) experienced tumor shrinkage. The stable disease rate at 8 weeks per RECIST was 5/13 (38%). The overall disease control rate was 38%.
- 48 in cohorts C and D – of this group, 15 patients (31%) experienced tumor shrinkage. The stable disease rate at 8 weeks per RECIST was 24/48 (50%), the objective response rate was 4/48 (8%), and the disease control rate was 28/48 (58%).

In total, of the 76 evaluable patients, the overall DCR at 8 weeks was 54% and the overall ORR was 5.3%.

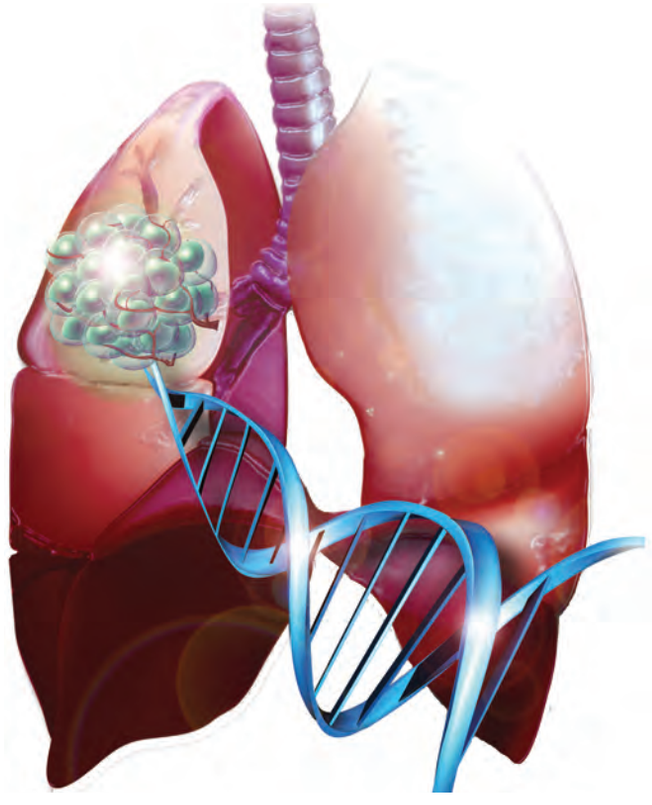
In addition, 23 of the 48 patients in cohorts C and D were subsequently tested for ALK translocation or rearrangement, and eight patients were found to be ALK-positive in at least one assay. Six of these eight patients (75%) showed tumor shrinkage in target lesions, one patient showed no change in tumor size, and one patient had tumor growth <20%. The disease control rate at 16 weeks in this population was 7/8 (88%), and the objective response rate (CR+PR) was 4/8 (50%).

The most common adverse event reported with ganetespib was diarrhea, which was generally mild-to-moderate in nature and manageable with supportive care. The dose-limiting hepatic and ocular toxicities seen with other Hsp90 inhibitors were absent in the case of ganetespib.

The investigators concluded that once-weekly ganetespib is well-tolerated in advanced NSCLC patients and shows promising clinical activity in these patients. It was also noted that all patients with durable objective responses had tumors with ALK rearrangement – further biomarker analysis is now taking place to identify genetic profiles sensitive to this treatment. In addition, a Phase IIb/III trial has now been initiated to examine ganetespib in combination with docetaxel.

"The evidence of clear single-agent activity combined with a favorable safety profile is exciting," concluded Dr Shapiro. "These results suggest ganetespib has the potential to provide a new therapeutic option for patients with advanced NSCLC."

Sources: Wong KK, Koczywas M, Goldman JW et al. An open-label Phase II study of the Hsp90 inhibitor ganetespib (STA-9090) as monotheraphy in patients with advanced non-small cell lung cancer. Presented at: Annual Meeting of the American Society of Clinical Oncology. Chicago, IL, USA, 3–7 June 2011; Synta Pharmaceuticals Press Release: http://ir.syntapharma.com/phoenix.zhtml?c=147988&p=irol-newsArticle&ID=1570819&highlight



NEWS

Highlights from the latest news and research in Clinical Investigation

FDA approves two new drugs for the treatment of hepatitis C

Boceprevir

The US FDA has announced the approval of Merck's first-in-class hepatitis C virus protease inhibitor, boceprevir (VICTRELIS) for the treatment of chronic hepatitis c (CHC)-genotype 1 infection. Boceprevir will be the first HCV protease inhibitor to reach the market and has been approved for use in combination with peginterferon alfa and ribavirin, the current standard therapy for CHC, in adult patients (18 years of age and older).

The safety and effectiveness of boceprevir was evaluated in two Phase III clinical trials with 1,500 adult patients. In both the HCV RESPOND-2 study (treatment-failure patients) and the HCV SPRINT-2 study, all patients receiving boceprevir were treated with a 4-week lead-in of peginterferon alfa-2b (1.5 mcg/kg/week) and an investigational dose of ribavirin (600-1,400 mg/day), followed by the addition of boceprevir (800 mg three times a day) after week 4. The results demonstrated that two-thirds of patients receiving boceprevir in combination with pegylated interferon and ribavirin experienced a significantly increased sustained virologic response rates compared to pegylated interferon and ribavirin alone. When a patient sustains a virologic response after completing treatment, this suggests that HCV infection has been cured.

"Compared to current standard therapy, VICTRELIS can significantly increase a patient's chance of achieving undetectable levels of the virus, thereby obtaining an SVR. For many patients, VICTRELIS may allow for a shorter total duration of treatment" explained Bruce Bacon, Professor of internal medicine, Saint Louis University School of Medicine, and a clinical investigator for VICTRELIS.

The most commonly reported side effects in patients receiving boceprevir include fatigue, anemia, nausea, headache and taste distortion.

"This is an exciting day for physicians and patients because VICTRELIS is the first major advancement for the treatment of chronic hepatitis C approved in a decade," enthused Bacon.

Sources: Approval of Victrelis (boceprevir) a direct acting antiviral drug (DAA) to treat hepatitis C virus (HCV):www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm255413.htm; FDA Approves Merck's VICTRELIS™ (boceprevir), First-in-Class Oral Hepatitis C Virus (HCV) Protease Inhibitor: www.merck.com/newsroom/news-release-archive/prescription-medicine-news/2011_0513.html?WT.svl=content&WT.pi=content+Views.

Telaprevir

Vertex Pharmaceuticals incorporated have announced the FDA approval of telaprevir (Incivek), making it the second drug following boceprevir to be approved for the treatment of hepatitis C in the last 20 years. Telaprevir has been approved for people with genotype-1 chronic hepatitis C with compensated liver disease, including cirrhosis. The approval follows the unanimous 18 to 0 vote by the Antiviral Drugs Advisory Committee on 28th April 2011, recommending that telaprevir be approved for this indication.

"Hepatitis C can lead to liver failure, cancer and the need for a transplant, and for the past decade, the best we could offer patients was a year of difficult treatment that resulted in a viral cure for fewer than half of them" explained Ira Jacobson, Chief of the Division of Gastroenterology and Hepatology, Weill Cornell Medical College and principal investigator for a Phase III study of telaprevir.

The safety and efficacy of telaprevir has been evaluated in three Phase III randomized trials conducted in a total of 2550 previously treated and untreated patients (1797 patients who received telaprevir combination treatment and 493 who received peginterferon alfa and ribavirin alone). In these studies, telaprevir was administered at a dose of 750 mg every 8 hours; the peginterferon alfa-2a dose was 180 µg/week, and the ribavirin dose was 800 mg/d in patients weighing less than 75 kg or 1200 mg/d in patients weighing 75 kg or more. Compared with the control group, receiving ribavirin plus pegylated interferon, the patients who also received telaprevir demonstrated a significantly higher rate of sustained virologic response of about 80% or more.

The sustained virologic response rate for patients treated with telaprevir across all studies, and across all patient groups, was 20 to 45% higher than the current standard of care. Achieving a sustained virologic response after completing treatment is believed to suggest that the hepatitis C infection has been cured. Sustained virologic response can result in decreased cirrhosis and complications of liver disease, decreased rates of liver cancer (hepatocellular carcinoma) and decreased mortality.

"With the approval of [telaprevir], there are now 2 important new treatment options for hepatitis C that offer a greater chance at a cure for some patients with this serious condition" pointed out Edward Cox, director, Office of Antimicrobial Products in FDA's Center for Drug Evaluation and Research in an agency press release. "The availability of new therapies that significantly increase responses while potentially decreasing the overall duration of treatment is a major step forward in the battle against chronic hepatitis C infection."

Sources: FDA Approves INCIVEK™ (telaprevir) for People with Hepatitis C: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=580154; FDA approves Incivek for hepatitis C: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm256299.htm