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Meeting Report

Take-home message: 2007 American Society of Clinical Oncology Annual Meeting

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Abstract

The 43rd American Society of Clinical Oncology (ASCO) Annual Meeting held in Chicago in early June served as a platform to stimulate dialogue between basic and clinical investigators and improve the "bench-to-bedside" and "bedside-to-bench" flow of research. The present report highlights important discoveries presented at the meeting and provides key points for different cancer types.

Introduction

The 43rd American Society of Clinical Oncology (ASCO) Annual Meeting held under the theme "Translating Research into Practice" took place in Chicago in early June 2007. It is more clear than ever not only that basic science must be translated into practical applications, but also that clinical research must provide observations to help guide and accelerate basic investigations. The ASCO Annual Meeting this year strived to catalyze the translational research in both directions: "bench-to-bedside" and "bedside-to bench". The extensive scientific and clinical content of the meeting was analyzed and prioritized, with important discoveries and developments becoming part of "ASCO 2007: take-home message", which continues the series of congress reports focusing on the most relevant information presented at international meetings.

Breast cancer

- Weekly paclitaxel is a preferable schedule in metastatic breast cancer
- No benefit of adding carboplatin to docetaxel/trastuzumab therapy in metastatic breast cancer
- Addition of ixabepilone to capecitabine improves progression-free interval but increases toxicity in metastatic breast cancer
- Lapatinib is active in patients with brain metastasis resulting from breast cancer
- Bevacizumab plus paclitaxel is the best first-line therapy for HER-2-negative breast cancer, although not yet approved by the FDA
- The NSABP B-31 study confirms trastuzumab-associated cardiotoxicity

Evaluation of 569 patients with metastatic breast cancer on either a weekly (n=278) or an every 3 weeks (n=291) regimen of paclitaxel revealed that the weekly schedule was associated with the same or better progression-free interval (24 weeks *versus* 22 weeks) and a better response rate (43% *versus* 33%). These results are similar to those observed in the CALGB 9840 study presented at the ASCO Annual Meeting in 2004. Therefore, weekly paclitaxel is the preferred schedule (1).

The BCIRG 007 study assessed the clinical benefit of adding carboplatin to trastuzumab/docetaxel therapy in HER-2-postive metastatic breast cancer patients. Time to progression, clinical benefit and complete and partial response rates were similar in both arms. Importantly, median survival time for both regimens was 3 years, likely the result of the addition of trastuzumab to chemotherapy. This study suggested that there is no additional benefit of carboplatin if the patients are already receiving docetaxel at 100 mg/m^2 (2).

Ixabepilone, an epothilone derivative, was evaluated in an international, randomized, open-label phase III trial in patients with metastatic or locally advanced breast cancer, with progression-free survival (PFS) being the primary endpoint. Ixabepilone (40 mg/m^2 by 3-h i.v. infusion every 3 weeks) plus capecitabine (2500 mg/m^2/day p.o. on days 1-14 every 3 weeks) resulted in a statistically significant improvement in PFS, although clinically the differ-

ence was only 6-7 weeks and the combination was more toxic when compared to capecitabine alone (3).

Lapatinib (750 mg b.i.d.) was active in patients (n=241) with HER-2-positive breast cancer and progressive central nervous system (CNS) disease who had undergone prior cranial radiotherapy and trastuzumab therapy. The results were encouraging, with partial responses registered in 6% of patients and reductions in lesion volume of 50% or more observed in 20% of patients. Grade 3 diarrhea, which is a common toxicity observed with lapatinib, was reported in 12% of patients (4).

Bevacizumab plus capecitabine was assessed as first-line therapy in 106 patients with HER-2-negative metastatic breast cancer. The progression-free interval was 5.7 months and complete and partial responses were obtained in 38% of patients (5). These results are comparable to those published by Miller *et al*. in the *Journal of Clinical Oncology* in 2005, where it was demonstrated that second-line bevacizumab plus capecitabine resulted in a progression-free interval of 5 months and a 20% response rate. However, recent data on bevacizumab plus paclitaxel presented at the San Antonio Breast Cancer Symposium by Miller *et al.* demonstrated a progression-free interval of 11.4 months, indicating that this may be the best first-line regimen.

Cardiac toxicity was reported to be the major toxicity associated with trastuzumab treatment of patients with HER-2-positive breast cancer. The NSABP B-31 study, which compared sequential doxorubicin/cyclophosphamide followed by paclitaxel *versus* doxorubicin/cyclophosphamide followed by paclitaxel with trastuzumab in patients with node-positive, HER-2-positive breast cancer provided further evidence that trastuzumab increases the incidence of chronic heart failure (CHF). The difference in the cumulative incidence of CHF at 5 years was 2.7% (6).

Gastrointestinal cancer

- Sorafenib extends survival in hepatocellular carcinoma
- Combinations of gemcitabine with cetuximab or bevacizumab do not add clinical benefit
- *CDH1* gene mutation predisposes for diffuse gastric cancer
- Perioperative FOLFOX4 improves PFS in patients with resectable colorectal cancer liver metastasis
- S-1 continues to show good results in gastric cancer

Sorafenib, a multikinase inhibitor, extended survival in patients with hepatocellular carcinoma (HCC), making it the most paradigm-changing presentation at this year's ASCO Annual Meeting. HCC is the third cause of death due to cancer, and currently no standard therapy exists for advanced HCC. In a multicenter, randomized, placebo-controlled phase III trial of sorafenib *versus* placebo in patients (n=602) with advanced HCC, significant improvement in overall survival was registered in patients receiving sorafenib: median overall survival was 10.7 months *versus* 7.9 months. Additionally, median time to progression was longer with sorafenib *versus* placebo (5.5 months *versus* 2.8 months). These findings establish sorafenib as a first-line treatment for advanced HCC (7).

Two phase III trials assessed combinations of biologics with gemcitabine in pancreatic cancer. In one study, gemcitabine alone or in combination with cetuximab was evaluated in patients with advanced pancreatic cancer. The objective response rates were similar in both arms (8). In another study, gemcitabine was combined with bevacizumab, but the lack of clinical benefit compared to gemcitabine alone resulted in termination of the study at interim analysis.

One of the prominent developments in gastric cancer is the discovery that mutation in the *CDH1* gene, which encodes the E-cadherin protein, increases the risk for gastric cancer. Prophylactic gastrectomy in 39 patients that tested positive for *CDH1* mutation revealed that 31 patients had occult diffuse gastric cancer (9).

Results from a randomized phase III study in patients with potentially resectable colorectal cancer showed that administration of perioperative FOLFOX4 chemotherapy improved PFS over surgery alone. Patients randomized to perioperative FOLFOX4 (6 cycles before and 6 cycles after surgery) had a significantly increased median PFS at a median follow-up of 3.9 years; the treatment was well tolerated (10).

S-1 is an orally available combination of tegafur, gimeracil and oteracil that has been used in Japan for several years for the treatment of stomach cancer. A study presented by Japanese investigators compared 5-fluorouracil (5-FU; continuous infusion) *versus* cisplatin plus irinotecan hydrochloride *versus* S-1 in patients with stomach cancer. It was found that S-1 was not inferior to infusional 5-FU and perhaps even better (11). Another group reported on a phase III trial of S-1 alone *versus* S-1 plus cisplatin in patients (n=106 and n=87, respectively) with advanced gastric cancer, termed the SPIRITS trial. S-1 had activity as a single agent (overall response rate was 31%), although combination of S-1 plus cisplatin produced better results (overall response rate of 54%) (12).

Genitourinary cancer

- Paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin showed no difference in overall survival in urothelial cancer
- Bevacizumab improves PFS when combined with interferon alfa-2a in metastatic renal cell carcinoma (mRCC)
- Satraplatin significantly reduces the risk of disease progression in hormone-refractory prostate cancer (HRPC)

A randomized, international phase III study evaluated the role of paclitaxel when added to gemcitabine with paclitaxel/cisplatin/gemcitabine in patients (n=627) with advanced/metastatic urothelial cancer, with the main endpoint being overall survival. Overall response rates were 57.1% for paclitaxel/cisplatin/gemcitabine and 46.4% for

paclitaxel/gemcitabine, and median PFS was 8.4 and 7.7 months, respectively. No significant difference in overall survival was found between the two treatment arms. Thrombopenia and bleeding were more common in patients on the paclitaxel/gemcitabine regimen (12% *versus* 7%), while paclitaxel/cisplatin/gemcitabine treatment caused more febrile neutropenia (13% *versus* 4%). Although paclitaxel/cisplatin/gemcitabine therapy produced better response rates, the endpoint for overall survival and PFS was not reached (13).

Bevacizumab in combination with interferon alfa-2a (IFN-α2a) as first-line treatment was found to benefit patients (n=649) with mRCC in a phase III trial. Overall, there were 505 progression events, 111 patients remained on treatment, 287 discontinued due to adverse events and 251 died. Patients on the bevacizumab plus IFN-α2a regimen had significantly better PFS (10.2 months *versus* 5.4 months) and objective tumor response rate (30.6% *versus* 12.4%). Moreover, there was a trend towards improved overall survival in the bevacizumab plus IFN-α2a arm (14).

Results from a randomized phase III trial revealed that satraplatin offers significant clinical benefits for the treatment of patients with HRPC. A total of 950 patients with HRPC who had failed prior therapy were administered either satraplatin (80 mg/m^2/day for 5 days every 5 weeks) plus prednisone or placebo plus prednisone. Satraplatin-treated patients had a significantly better prostate-specific antigen (PSA) response (25% *versus* 12%), objective tumor response (7% *versus* 1%) and pain response (24% *versus* 14%). Patients in the satraplatin arm had a significantly lower risk of disease progression and final analysis of overall survival awaits the occurrence of the prespecified number of events (15).

Gynecological cancer

- Maintenance chemotherapy does not benefit overall survival in advanced ovarian cancer
- Pegylated liposomal doxorubicin is better tolerated than gemcitabine in recurrent ovarian cancer
- TLK-286 efficacy was not confirmed in chemotherapy-resistant ovarian cancer
- VEGF Trap is active in platinum-resistant ovarian cancer
- Adjuvant radiotherapy plus chemotherapy improves PFS and overall survival in high-risk endometrial cancer

A phase III trial conducted by Italian researchers compared observation *versus* 6 courses of paclitaxel in patients with advanced ovarian cancer in complete response after platinum/paclitaxel chemotherapy. No differences in PFS or overall survival were found, further confirming results from previous studies indicating that maintenance chemotherapy does not offer additional benefit (16).

Randomization of 154 patients with recurrent ovarian cancer to either gemcitabine (1000 mg/m^2 on days 1, 8, 15 and 28) or pegylated liposomal doxorubicin (40 mg/m^2 for 28 days) in a study by the MITO group revealed no difference in time to progression between the two arms. However, gemcitabine was associated with more hematological toxicity and pegylated liposomal doxorubicin with better quality-of-life scores; overall survival data are not yet available (17).

One of the major obstacles in treating ovarian cancer is resistance to chemotherapy. Canfosfamide hydrochloride (TLK-286), a glutathione *S*-transferase (GST)-activated prodrug of a phosphorodiamidate alkylating agent, was evaluated in two trials, the ASSIST-1 and ASSIST-3 studies, in patients with recurrent ovarian cancer. Previous reports have indicated that TLK-286 is capable of reversing cisplatin resistance. The ASSIST-1 trial (third-line treatment) in 440 patients randomized to TLK-286, pegylated liposomal doxorubicin or topotecan revealed that patients in the TLK-286 arm had worse overall survival than those in the doxorubicin or topotecan arms: 8.5 months *versus* 14.2 and 10.8 months, respectively. In the ASSIST-3 study (second-line treatment), no differences in PFS were observed between patients randomized to TLK-286 plus carboplatin or pegylated liposomal doxorubicin arms (18).

VEGF Trap (aflibercept) is a fusion protein with high affinity for vascular endothelial growth factor (VEGF). Results from an ongoing phase II study of VEGF Trap (2 mg/kg *versus* 4 mg/kg i.v. every 2 weeks) in 162 patients with platinum-resistant ovarian cancer showed stable disease or partial responses in 41% of patients; however, the drug was associated with grade 3-4 toxicities (hypertension, gastrointestinal perforation and proteinuria) and the optimal dose has not been chosen (19).

Hogberg *et al.* presented results of the randomized phase III trial of adjuvant radiotherapy with or without chemotherapy in patients (n=382) with early-stage high-risk endometrial cancer. Addition of chemotherapy increased PFS from 74% to 83% and overall survival from 78% to 88%. Nevertheless, one of the major limitations of this study was the lack of standardization of chemotherapy — patients were administered carboplatin, paclitaxel, doxorubicin, cisplatin or epirubicin, or a combination of these agents (20).

Head and neck cancer

- Addition of cetuximab to first-line platinum-based therapy extends survival in patients with recurrent and/or metastatic squamous cell head and neck cancer (SCCHN)
- Combination of cetuximab and weekly paclitaxel is beneficial in recurrent and/or metastatic SCCHN
- Erlotinib in combination with chemotherapy shows encouraging activity in incurable SCCHN
- Axitinib shows beneficial activity in patients with advanced thyroid cancer
- Human papillomavirus (HPV) status of oropharyngeal tumors is of prognostic significance

Data from an international, multicenter, randomized phase III study (the EXTREME study) in patients (n=442)

with recurrent or metastatic SCCHN showed that addition of cetuximab to first-line platinum-based therapy (cisplatin or carboplatin) produced a significant benefit in overall survival (median overall survival prolonged by 2.7 months). This was the first study in 25 years to report the beneficial use of an agent other than platinum-based therapy in recurrent or metastatic SCCHN, and will likely have an impact on the standard of care for these patients. The results for secondary endpoints, such as quality of life, are still being evaluated (21).

The Spanish Head and Cancer Group (TTCC) presented initial results of a phase II study assessing the combination of cetuximab (400/250 mg/m^2 i.v. weekly) and paclitaxel (80 mg/m^2 i.v. weekly) in patients (n=42) with recurrent and/or metastatic SCCHN. Complete and partial responses were seen in 10 and 15 patients, respectively, with a PFS of 5 months and time to progression of 6.2 months. This study continues patient accrual, and these preliminary data suggest that the addition of cetuximab is beneficial in metastatic and/or recurrent SCCHN (22).

A phase II study assessing erlotinib (100 or 150 mg/day p.o.), docetaxel (60 or 75 mg/m^2 i.v. every 3 weeks) and cisplatin (75 mg/m^2 i.v. every 3 weeks) in patients (n=48) with recurrent and/or metastatic SCCHN had the overall response rate as a primary endpoint. Complete and partial responses were registered in 4 and 28 patients, respectively, with an overall response rate of 66% and a disease control rate of 91%. Moreover, only 3 patients progressed after 2 cycles of treatment, and median overall survival was 11 months. The positive results of this first study evaluating the combination of erlotinib with chemotherapy suggest that further investigation of this regimen in incurable SCCHN is warranted (23).

HPV, especially the "high-risk" type HPV-16, has been associated with the development of SCCHN. Scientists from Johns Hopkins University studied the effect of HPV infection on survival and treatment responses in patients with SCCHN. Induction chemotherapy with paclitaxel and carboplatin followed by concurrent chemoradiotherapy was chosen as a treatment regimen. HPV was detected in 61% of patients with oropharyngeal cancer, while patients with laryngeal cancer were HPV-negative. HPV-positive patients showed a better response to induction therapy and had a clear benefit in overall survival, suggesting that HPV status could be used as a prognostic factor (24).

Leukemia, myelodysplasia and transplantation

- Fludarabine/cyclophosphamide/rituximab has major activity in chronic lymphoblastic leukemia (CLL)
- MicroRNA and gene expression signatures have prognostic utility in acute myeloid leukemia (AML)
- Dasatinib 100 mg/day p.o. may be the best dose
- Nilotinib and bosutinib are active in chronic myelogenous leukemia (CML)
- Nilotinib, bosutinib and dasatinib have comparable efficacy

Investigators from the M.D. Anderson Cancer Center have demonstrated in a phase II trial in 300 patients with CLL that a fludarabine/cyclophosphamide/rituximab (FCR chemo/immunotherapy) regimen is associated with a 72% complete response rate, a 70% PFS rate at 5 years and a median time to progression of 80 months. There was a small increased risk of myelodysplastic syndrome (MDS) at 5 years and those who progressed on this treatment had a poor prognosis with salvage therapy (25, 26). A phase II study, known as CALGB 10404, is under way to test combinations of fludarabine/rituximab *versus* fludarabine/cyclophosphamide/rituximab *versus* fludarabine/rituximab/lenalidomide.

Over the years, prognostic features of AML have expanded from age and cytogenetic status of the patient to genetic mutations in *FLT3, KIT, CEBP* and *BCL2* and, presently, genetic signatures. Two studies assessed the use of gene expression profiles in AML. One study demonstrated that microRNA signatures correlated with mutations in *FLT3, ERG* and *NPM* genes and corresponded to prognosis in younger adults with AML with normal cytogenetics. Another study in AML patients with t(8; 21) translocation, which confers a good prognosis, showed that patients with good cytogenetics could be further subdivided according to their genetic profile into unfavorable and favorable subgroups (27, 28).

In chronic CML, imatinib and dasatinib are the current standards of pharmacological therapy. A study sponsored by Bristol-Myers Squibb evaluated the best dose of dasatinib (100 mg/day, 50 mg/day, 140 mg/day or 70 mg b.i.d.) to use in patients who are intolerant or resistant to imatinib. Response rates were comparable in all four arms; however, patients on 100 mg/day experienced less neutropenia, thrombocytopenia, anemia and pleural effusion (29). In a phase II study conducted by researchers at the M.D. Anderson Cancer Center, newly diagnosed patients (n=31) with CML were administered dasatinib either at 100 mg/day or 50 mg b.i.d. There was a 95% complete cytogenetic response rate and a 27% major molecular response rate at 12 months. Although these results are very encouraging, it is still premature to recommend dasatinib as first-line therapy due to excellent long-term results with imatinib (30).

Novartis' kinase inhibitor nilotinib produced major cytogenetic responses in 52% and complete cytogenetic responses in 34% of patients with imatinib-intolerant or -resistant CML (n=316) at 6 months of treatment. Nilotinib also caused grade 3-4 adverse events and it is still unclear how this drug will be used, if approved, since the response rates are similar to those of dasatinib (31). Another tyrosine kinase inhibitor, bosutinib, from Wyeth was found to be well tolerated (grade 3-4 toxicities observed in only 5% of patients) in a phase I/II study, eliciting response rates similar to dasatinib and nilotinib. A major cytogenetic response was observed in 52% of patients who were intolerant or resistant to imatinib (32). In conclusion, since dasatinib, nilotinib and bosutinib all seem to have similar efficacy, the choice of the agent to use in cases of imatinib failure will depend on the side

effect profile and specific mutations in the Bcr-Abl kinase.

Lung cancer

- Gefitinib is not inferior to docetaxel in terms of overall survival in non-small cell lung cancer (NSCLC)
- Gefitinib does not benefit patients with stage III NSCLC
- Docetaxel consolidation therapy does not improve survival in stage III NSCLC
- Bevacizumab prolongs PFS in the AVAiL study
- Preoperative and postoperative chemotherapy improves survival
- Carboplatin/irinotecan is as effective as carboplatin/etoposide in small cell lung cancer (SCLC)
- Vandetanib maintenance does not offer any additional survival benefit in SCLC
- Bevacizumab does not add benefit to chemotherapy in malignant mesothelioma

A Japanese phase III study in patients with previously treated advanced NSCLC compared gefitinib (Iressa®) at 250 mg/day to docetaxel (60 mg/m^2 every 3 weeks). Median survival on gefitinib was 11.5 months *versus* 14 months on docetaxel and 1-year survival was 48% and 54%, respectively. Statistical analysis of these data demonstrated that gefitinib was not inferior to docetaxel in terms of overall survival (33).

Another study of gefitinib in patients with locally advanced inoperable stage III NSCLC showed that randomization to gefitinib maintenance therapy (250 or 500 mg/day) after treatment with chemo- and radiotherapy and 3 cycles of docetaxel consolidation therapy produced worse results than the placebo arm in terms of overall survival (23 and 35 months, respectively). There were more cancer-related deaths in the gefitinib arm when compared to placebo (61 patients *vs.* 43 patients), leading the authors to suggest that gefitinib-mediated modification of epidermal growth factor receptor (EGFR) signaling may be implicated in this outcome (34). One of the reasons for survival being worse in patients on gefitinib could be attributed to its ability to activate some oncogenic drivers in the tumors of patients who were exposed to long-term gefitinib therapy.

Results from a phase III trial of cisplatin/etoposide and concurrent chest radiation with or without docetaxel (75 mg/m^2 every 3 weeks for 3 cycles) consolidation in patients with inoperable stage III NSCLC revealed that PFS and overall survival did not differ. However, toxicity was much greater in patients who were randomized to docetaxel: grade 3-4 infection in 11% *vs.* 0%, grade 3-4 pneumonitis in 9.6% *vs.* 1.4% and hospitalization in 28.8% *vs.* 8.1%. In conclusion, docetaxel consolidation therapy does not improve survival and is associated with a significantly higher rate of toxicities (35).

The ECOG 4599 study, which was presented 2 years ago, demonstrated significantly improved survival in patients with NSCLC on bevacizumab. This year, the AVAiL trial, a phase III randomized study in previously untreated stage IIIb/IV or recurrent non-squamous cell NSCLC without brain metastasis or tumor invasion into major blood vessels, revealed that bevacizumab (7.5 or 15 mg/kg every 3 weeks) improved PFS compared to placebo. The data are still premature to analyze overall survival, and the incidence of serious adverse events leading to death was comparable across the three arms, although a higher incidence of hypertension was seen in patients on bevacizumab (36).

The Norwegian Lung Cancer Group reported the outcomes of a phase III trial of pemetrexed/carboplatin *versus* gemcitabine/carboplatin as first-line chemotherapy in patients with stage IIIB/IV NSCLC. Although there was no difference in survival, the incidence of toxicities was lower in patients treated with pemetrexed/carboplatin, resulting in a decrease in the number of blood transfusions (37).

A four-arm phase III study compared pre- and perioperative chemotherapy with two different chemotherapy regimens (gemcitabine/cisplatin or paclitaxel/carboplatin) in resectable NSCLC. Postoperative mortality was low in both pre- and perioperative arms, compliance was better in the preoperative arm, no differences in pathological responses were observed after 2 or 4 cycles and higher response rates were registered in patients with squamous cell cancers when compared to other histological types of cancer. It is feasible to administer 4 cycles of chemotherapy in a preoperative setting (38). Results from another phase III study, the SWOG 9900 trial, demonstrated that preoperative paclitaxel/carboplatin chemotherapy in early-stage NSCLC improved PFS and overall survival when compared to surgery alone (39).

In SCLC, results from a Norwegian phase III trial of irinotecan hydrochloride plus carboplatin *versus* etoposide plus carboplatin indicate that the former is associated with more responses (18 patients *vs.* 7 patients) and better median survival (8.5 months *vs.* 7.1 months). In accordance with previous data, these two regimens can be considered to have comparable efficacy (40). Another study in SCLC patients revealed that vandetanib maintenance did not make a difference in PFS or overall survival after vandetanib induction therapy (41).

Final results from a multicenter, double-blind phase II trial in patients with malignant mesothelioma showed that addition of bevacizumab to a gemcitabine/cisplatin regimen did not improve overall survival (42). No benefit in terms of overall survival was found in a phase III study of active symptomatic control with or without chemotherapy in patients with mesothelioma. These findings were surprising, since previous studies had shown that chemotherapeutic regimens are active in mesothelioma (43).

Melanoma

- Prolonged interferon therapy does not improve survival in stage III melanoma
- Interferon triggers production of autoimmune antibodies
- Vaccines continue to be tested
- Sorafenib prolongs time to progression in stage IV melanoma

Once melanoma reaches stage III/IV, the treatment options are scarce and the prognosis is bleak. This year, presentations at the ASCO Annual Meeting focused on the treatment of advanced melanoma: stage III disease with immune therapies such as interferon alfa and vaccines, and stage IV disease with combinations of chemotherapy and targeted agents.

The current standard of treatment for stage III melanoma is high-dose interferon therapy (1-month induction i.v. plus 48 weeks s.c.). A study from Eggermont *et al*. demonstrated that treatment of patients with interferon for 5 years produced a similar advantage in terms of relapse-free survival, but did not prolong overall survival when compared to the observation arm. Moreover, interferon therapy is associated with considerable toxicity, 40% of patients withdrawing from this study due to toxicity (44).

One of the presentations analyzed the mechanism of action of interferon in melanoma. The investigators tested blood samples from stage III melanoma patients (n=278) for the presence of anti-cardiolipin, anti-thyroglobulin and anti-nuclear antibodies. Although it was found that interferon induces the production of autoimmune antibodies, the correlation between the presence of such antibodies and PFS depended on the type of statistical analysis used to evaluate the data (45).

A phase III trial of Bacillus Calmette-Guerin (BCG) and allogeneic melanoma vaccine (MCV) administered every 2 weeks to 3 months for up to 5 years or placebo showed no differences in survival in patients with stage III (n=1,160) and IV (n=496) melanoma (46). Several studies are currently under way to test the combination of vaccines and interferon.

For patients with stage IV melanoma, several studies evaluated targeted agents as potential therapeutic approaches. A randomized phase II trial of sorafenib (400 mg p.o. b.i.d.) *versus* placebo in previously untreated stage IV melanoma patients on decarbazine therapy showed that sorafenib prolonged the time to progression but not overall survival (47). Results from a phase III study conducted in 270 patients with stage III/IV melanoma randomized to receive either carboplatin/paclitaxel/sorafenib or carboplatin/paclitaxel/placebo demonstrated no differences in overall survival (48). It is hoped that further understanding of the tumor microenvironment and mechanisms of action of immunotherapies will allow beneficial combinations with targeted agents.

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