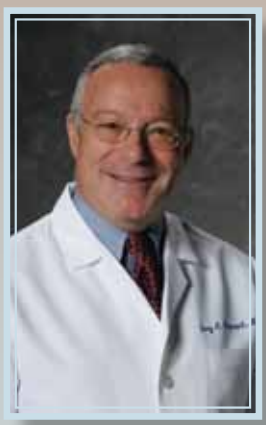
Best of ASCO 2011

Perspectives from a community oncologist

by Cary A. Presant, MD, FACP



The 2011 ASCO meeting centered around the evolution of medical oncology practice by incorporating gene-directed therapies. There were many discussions about this topic, and the emphasis in future years will be on biomarker determinations in association with all clinical trials. This paradigm shift will add to the expense and burden of clinical trials performance, but hopefully aid in the selection of appropriate therapy for individual patients. In a discussion about this genetic revolution, Harold Varmus, MD, Director of the National Cancer Institute (NCI), pointed to the increase in clinical trials that will be needed, and the increase in genetic testing already required for optimal patient care. Dr. Varmus has said he will discuss both with the Centers for Medicare & Medicaid Services (CMS). He has also started a "provocative questions" initiative to focus research activities on new and important areas.

George W. Sledge, Jr., MD, President of ASCO, discussed the state of oncology care and emphasized the poor success of Phase II studies (29 percent) and Phase III studies (34 percent) in terms of either failure to reach end points or failure to enroll a sufficient numbers of patients. He also pointed out the poor success of therapy in many tumor types, and he related this situation to the occurrence of "dumb" cancers (low mutation rate), which are responsive to therapy, and "smart" cancers (with high mutation rates), which are resistant to therapy. In general, we have been successful if there is less than one mutation per megabase, but highly unsuccessful if there are more than 100 mutations per megabase in the tumor cell genome. In non-small cell lung cancer (NSCLC), a tumor with a high mutation rate, there is one mutation for every three cigarettes ever smoked. Dr. Sledge has committed ASCO to a rapid learning system in oncology, and it is a challenge as to how oncologists will become involved with this initiative.

The following are highlights from ASCO 2011. It is my belief that bold abstracts marked with an asterisk will change the standard of practice.

Non-Small Cell Lung Cancer

- *Abstract 7507** compared crizotinib therapy of ALK-positive tumors versus non-crizotinib therapy. Crizotinib produced an increased overall survival (HR 0.36), with a 2-year overall survival of 55 percent in second- and third-line therapy.
- *Abstract 7500* identified the first clinical activity of an Hsp90 inhibitor. In patients who had failed prior therapy, ganetespib produced 7 partial responses in 73 patients.
- *Abstract 7501* tested a toll-like receptor-2 agonist Cadi-05. In a Phase II randomized study, there was an increased PFS (HR 0.69, P=0.05).
- ***Abstract 7503**** showed that in patients with EGFR mutations (21 percent of NSCLC) erlotinib was superior to a platinum doublet (DFS HR 0.37, median 9.4 versus 5.2 months).
- *Abstract CRA 7506* described a multi-institutional network that had been developed to perform molecular analyses on all NSCLC patients. In their first cohort, 516 patients (46 percent) had no mutations. Fifty-four percent had mutations, with one exclusive mutation in 97 percent. At Memorial Sloan-Kettering Cancer Center, 30 percent of all patients evaluated went on a matched drug trial.

Small Cell Lung Cancer

- ***Abstract 7000**** compared amrubicin with topotecan. Amrubicin was superior, with a longer overall survival (HR 0.82, P=0.036).

Breast Cancer

- *Abstract 500* showed that the addition of Xeloda to AC followed by T produced better DFS (HR 0.7) in patients whose Ki-67 was over 10 percent.
- ***Abstract LBA 504**** showed that exemestane prevented new breast cancers. The HR was 0.47 for all cancers, and 0.35 for invasive breast cancer (P=0.002), and the cancers prevented were ER positive, and both HER-2 positive and HER-2 negative.
- *Abstract 507* showed that neoadjuvant lapatinib plus trastuzumab in HER-2 positive patients showed an increased pathological CR rate of 43 percent versus only 26 percent for trastuzumab alone.
- *Abstract 509* found that in patients with HER-2 positive breast cancer with brain metastases, lapatinib plus capecitabine showed a 67 percent response rate in 45 patients, remarkably with no radiation therapy given.
- ***Abstract LBA 1003**** showed that in patients with node positive breast cancer with one to three positive nodes, the addition of radiation therapy to the internal mammary and supraclavicular nodes produced an increased DFS (HR 0.59, P=0.02), but with a decreased satisfactory cosmetic outcome at 5 years (36 percent dissatisfied after RT versus 29 percent without RT). There was a decrease in distant metastases of 8.4 percent versus 12.7 percent without RT.
- *Abstract 1007* found that iniparib with gemcitabine and carboplatin produced a slight increase in DFS (5.1 ver-

Acronym ABCs

- ASCT: autologous stem cell transplant
- ADT: androgen deprivation therapy
- CR: complete response
- DFS: disease-free survival
- DVT: deep vein thromboembolism
- EFS: event-free survival
- FDA: Food and Drug Administration
- HR: hazard ratio
- HRT: hormone replacement therapy
- PFS: progression-free survival
- RFS: relapse-free survival
- RT: radiation therapy
- TVU: transvaginal ultrasound
- VTE: venous thromboembolism

sus 4.1 months median) with an HR of 0.79 (P=0.027). This result was unexpectedly poor compared to expectations from ASCO 2010.

- *Abstract 1010* discussed the results of the RIBBON-2 study showing that various chemotherapies when combined with bevacizumab had an increased PFS of 6.0 versus 2.7 months (HR 0.49, P=0.0006).
- ***Abstract 1500**** showed that tamoxifen prevents second cancers in women with *BRCA1* mutations (HR 0.52) or *BRCA2* mutations (HR 0.39).
- *Abstract 1501* found that patients with *BRCA1* and *BCRA2* mutations with risk-reducing salpingo-oophorectomy (RRSO) who also received hormone replacement therapy (HRT) did not have any increased breast cancers as a result of the HRT. This finding indicates that HRT is safe following RRSO in patients with *BRCA* mutations.
- ***Abstract 1511**** showed that when women had rapid *BRCA1* and *BRCA2* testing following the diagnosis of breast cancer, the finding of a mutation resulted in an increased choice by the women for bilateral mastectomy in 52 percent, versus only 5 percent if the *BRCA1* and *2* testing was negative. This finding suggests that rapid *BRCA1* and *2* testing should be offered to patients to help them make a decision regarding primary surgical therapy.
- *Abstract 1510* found that paternal inheritance of *BRCA1* or *2* mutations was associated with a younger age at diagnosis of breast cancer and ovarian cancer.
- *Abstract 1513* showed that routine *BRCA 1* and *2* testing in all Ashkenazi Jewish women showed frequent abnormal mutations. Remarkably, 63 percent of these women did not have a positive family history. This finding argues for routine testing in all Ashkenazi Jewish women.
- *Abstract 1514* found that 25 percent of Hispanics with breast cancer showed a mutation in *BRCA 1* or *2* with a founder mutation being very frequent. This finding supports screening all Hispanic women with breast cancer and any family history.

Head and Neck Cancer

- *Abstract 5500* discussed RTOG 0522, and showed that if patients received radiation therapy plus cisplatin, addition of cetuximab produced no increase in PFS or overall survival.

Malignant Melanoma

- ***Abstract LBA 4**** showed that melanoma patients with BRAF V600E mutations (45 percent of melanoma patients) had good responses when treated with the BRAF inhibitor vemurafenib. In stage IV patients, 90 percent had some type of response with 48 percent having complete or partial responses. This result was superior to use of DTIC for overall survival (HR 0.37, P=0.0001) and for PFS (HR 0.26, P=0.0001).
- ***Abstract LBA 5**** found that ipilimumab was superior to therapy with DTIC alone, with an increase in overall survival (HR 0.72, P=0.0009) and an increase in PFS (HR 0.76, P=0.0006).
- ***Abstract 8506b**** showed the results of EORTC 18991. Using pegylated interferon alpha 2b (Sylatron) as adjuvant therapy, results were superior compared to no adjuvant treatment, with an improvement in relapse free survival (HR 0.87, P=0.05) and this was best in patients with stage III cancers, ulcerated tumors, and/or positive nodes.
- *Abstract 8519* indicated that patients should continue vemurafenib if there is only progression in one or several metastases (oligoprogression), since disease control continued.
- *Abstract 8548* showed that vemurafenib produces responses in brain metastases.
- *Abstract 8509* discussed vemurafenib in previously treated patients with BRAF-mutant melanoma and showed a 52.3 percent partial response rate with a median duration of response at 6.2 months.

Non-Hodgkin Lymphoma

- *Abstract 8000* showed that R-CHOP every 14 days was equivalent to R-CHOP every 21 days.
- ***Abstract 8001**** found that in treatment of diffuse large B-cell lymphoma, R-CHOP plus autologous stem cell transplant (ASCT) in patients with high IPI scores, there was an increased 2 year PFS (75 percent versus 41 percent without ASCT), and an increased 2 year overall survival (82 percent versus 64 percent without ASCT). Both curves appear to have plateaued.

Sarcoma

- ***Abstract LBA 1**** showed that after resection of GIST tumors, adjuvant imatinib was better for 36 months compared to 12 months with an overall survival improvement (HR 0.45, P=0.019) and an increase in progression-free survival (HR 0.46, P=0.0001). The effects correlated with differences in c-kit and PDG-FRA mutations, so molecular testing should become standard in this disease.
- ***Abstract LBA 10002**** found that patients with soft tis-

Abstract LBA 5006* showed that addition of bevacizumab to primary chemotherapy in the ICON7 study resulted in a borderline improvement in overall survival...

sue sarcoma progressing after chemotherapy improved after therapy with the angiogenesis inhibitor pazopanib with an increased PFS compared to placebo (HR 0.31, P=0.0001).

- *Abstract 10005* tested the mTOR inhibitor ridaforolimus in the SUCCEED trial. If the patient had stable disease or response on prior chemotherapy, the addition of the mTOR inhibitor as maintenance therapy was superior to placebo with a median control of 17.7 versus 14.6 months (HR 0.72, P=0.0001).

Prostate Cancer

- ***Abstract 4514**** investigated intermittent androgen deprivation therapy (ADT). The use of intermittent ADT after radical radiotherapy was not inferior to continuous therapy for localized prostate cancer in terms of overall survival (8.8 years with intermittent versus 9.1 years with continuous). However, as intermittent ADT improved several quality-of-life measures and is more cost-effective than continuous ADT, researchers believe that this trial will change clinical practice. The downside: monitoring these patients is more intensive because, in their off-treatment period, you have to continue to monitor PSA every 2 or 3 months.
- *Abstract 4516* investigated cabozantinib, which is an inhibitor of MET and VEGFR 2. In this study, there was a 74 percent reduction in tumor size with 4 percent partial response and 79 percent stable. Bone scan was incredibly and remarkably improved with 19 percent complete response and 56 percent partial response with a reduction in pain of 70 percent. This important new investigational treatment will hopefully be fast-tracked by the FDA.

Colon Cancer

- *Abstract 3507* reported on the use of oxaliplatin adjuvant therapy in stage II patients in NSABP studies C05 through C08. Oxaliplatin with 5-FU and leucovorin did not significantly increase overall survival in stage II colon cancer but it was numerically higher by 3 to 5 percent compared to 5-FU and leucovorin. There was controversial discussion with some discussants emphasizing that this small benefit was enough to consider using oxaliplatin, but the results were not highly impressive.
- *Abstract 3510* evaluated panitumumab in wild-type *KRAS* tumors. There was an increase in PFS. More importantly, there was an increase in complete response after liver resection from 10 percent to 17 percent.
- *Abstract 3511* examined a unique mutation KRAS 613D. There was a non-significant trend for patients with metastatic colon cancer in the CRYSTAL and OPUS studies who had mutant KRAS 613D to benefit from cetuximab plus chemotherapy (response rate 40.5 percent versus 22 percent without cetuximab, p= 0.07). However, there was only a marginal increase in PFS (7.4 months versus 6.0 months, p= 0.10) and no difference in OS. Patients with this mutation may be candidates for cetuximab if differences are confirmed and become significant.
- *Abstract 3531* showed an important correlation between low VEGF D (determined by IHC) in the tumor and response to bevacizumab (P=0.02). This data may be a clue to a reliable biomarker for bevacizumab responsiveness.

Ovarian Cancer

- *Abstract 5001* evaluated CA-125 and transvaginal ultrasound (TVU) for ovarian cancer screening. There was no decrease in deaths, but there was an increase in complications due to false positives. In the biomarker discussion Dr. Bast said that screening with a rising CA-125 level prompting subsequent TVU resulted in a two-fold increase in detection of stage I and II cancers.
- *Abstracts 5003 and 5004* evaluated olaparib in ovarian cancer. The drug was found to be active by both investigators. In a study looking at maintenance olaparib after chemotherapy, Ledermann found an increased PFS during maintenance olaparib (HR 0.35, P=0.0001). Olaparib was found to be active by Penson in both *BRCA 1, 2* wild type or *BRCA 1, 2* mutations.
- ***Abstract LBA 5006**** showed that addition of bevacizumab to primary chemotherapy in the ICON7 study resulted in a borderline improvement in overall survival (HR 0.84, P=0.09), but in poor prognosis patients it was more effective (overall survival HR 0.64, P=0.002).
- ***LBA 5007**** studied recurrent ovarian cancer. The addition of bevacizumab to gemcitabine plus carboplatin resulted in a longer PFS (HR 0.48, P=0.001), but no impact yet on overall survival (HR 0.71 but P=0.09).

Leukemia

- ***Abstract 6500**** discussed the COMFORT-1 study. The JAK2 inhibitor ruxolitinib was used in myelofibrosis. There was a 42 percent reduction in spleen size versus 0.7 percent with placebo (P=0.0001). Symptom improvement was superior with ruxolitinib compared to placebo (46 percent versus 5 percent, P=0.0001). These studies were confirmed in COMFORT-2 with a reduction in spleen volume of 29 percent when compared to best available therapy (P=0.0001).
- *Abstract 6503* studied AML. Overall survival was not different when clofarabine was added to cytarabine. The response rate was higher for the combination, 47 percent

versus 23 percent, and the event-free survival at four months was better at 38 percent compared to 17 percent.

Myeloma

- *Abstract 8010* looked at the impact of zoledronic acid. Overall survival was only increased if bone disease was present at initiation of therapy. In that circumstance, overall survival was improved with the addition of zoledronic acid by 5.5 months (P=0.01).
- *Abstract 8011* studied zoledronic acid and examined patients at initiation of chemotherapy. The addition of zoledronic acid was found to be superior to clodronate (increased PFS, P=0.002).

General Oncology:

- *Abstract 1000* evaluated ECOG study 5103. A genome-wide association study was performed and demonstrated that the stress response gene RWDD3 polymorphism was associated with neuropathy. Wild type had only 27 percent neuropathy, whereas VV had 60 percent neuropathy.
- ***Abstract 1503**** looked at the association of metformin with breast cancer. Women taking metformin in the Women's Health Initiative (WHI) had a reduction in ER positive cancer of the breast by 38 percent (P=0.02).
- *Abstract 1538* studied gestational diabetes. Women who had gestational diabetes had a 7-fold increased risk of pancreatic cancer and 1.7-fold increase in hematologic malignancies.
- *Abstract 9024* showed that the addition of talactoferrin alfa (used as an oral immunomodulator) improved the outcome of patients with sepsis. The talactoferrin was taken orally 3 times a day for 28 days. Mortality was reduced from 26.9 percent without talactoferrin down to 14.4 percent with talactoferrin.
- *Abstract CRA2500* evaluated molecular analyses on patients entering Phase I studies at MD Anderson Hospital. In 995 patients, 852 had molecular analysis feasible. Forty-two percent had one or more mutations. If there was only one mutation, and a matched therapy which targeted that mutation was used, time-to-treatment failure was prolonged, 5.3 months versus 3.2 months in controls (P=0.0003). This finding substantiates the value of doing molecular analyses, but the benefits are small and affect only a small number of patients.

Survivorship

- *Abstract 6007* showed that patients who had a cancer diagnosis had 2.1 percent risk of bankruptcy by 4.5 years. The risk was increased if patients were under 65 years old (2- to 3-fold increase). The median time to bankruptcy was 2.5 years and the highest frequency was in lung cancer patients.
- *Abstract 9005* looked at a survival care plan for breast cancer given to the patient with an oncology nurse conference, versus a standard discharge letter and visit. There were no differences in psychosocial adjustment, continuity of care, or quality of life, suggesting low impact on those variables by a survivor care plan.
- *Abstract 9008* demonstrated post-chemotherapy cerebral dysfunction in 25 percent of women. This finding was associated with an increase in soluble TNF receptor-type 2 and also with abnormalities in functional PET scanning, which was located in the pre-frontal area.
- ***Abstract 9026**** examined vitamin D replacement in women undergoing aromatase inhibitor therapy. Increasing the vitamin D levels to over 40 mg/mL prevented AI associated bone loss (this required 800 to 2000 IU per day).
- *Abstract 9032* showed that patients with low albumin under 3.5 predicted increased frequency of VTE (12.5 percent if under 3.5, 6 percent, if over 3.5).
- ***Abstract 9034**** looked at yoga after adjuvant chemotherapy. Gentle Hatha and restorative asanas (postures) twice a week for 4 weeks resulted in reduced anxiety, increased mood, and improvement in circadian rhythm.
- *Abstract 9035* found that 10 weeks of medical Qigong (exercise and meditation) resulted in improved cognitive function and increased quality of life.
- *Abstract 6008* found that pain control was poor in cancer patients. Sixty-seven percent of patients with cancer of the breast, colon, lung, or prostate required analgesics or complained of pain. Twenty percent of all patients listed their pain control as inadequate and not improving with time. Minority cancer patients were 2-fold more likely to have inadequate control.
- *Abstract LBA 9014* looked at an ultra-low molecular weight heparin semuloparin. In patients with cancer of the lung, colon, stomach, ovary, pancreas, or bladder who were receiving chemotherapy, the frequency of DVT or PE was reduced from 3.4 percent to 1.2 percent (HR 0.36, P=0.0001) with no change in major bleeding.

If you are interested in any or most of these highlights, I recommend you review the complete abstract on ASCO's website (*www.asco.org*).

Cary A. Presant, MD, FACP, is a past president of the Association of Community Cancer Centers. He has also served on the Board of Directors of the American Society of Clinical Oncology and is currently Chairman of the Board of the Medical Oncology Association of Southern California. He is a medical oncologist at Wilshire Oncology Medical Group in Los Angeles, Calif.