ASCO Round-up: Clinical Application of Recent Data

Perspectives from oncologists in the outpatient oncology clinic

by Ann L. Mellott, MD, and Mary F. Mulcahy, MD

Over time, results of the 2007 ASCO studies may prove to be of clinical significance, scientific significance, or a building block to advance the field. Following are highlights of pertinent studies that may affect cancer treatment *today*.

Breast Cancer: Adjuvant Therapy

As seen with trastuzumab, clear pros and cons of therapy exist and must be carefully discussed with each patient. *Abstract LBA513* presented the 5-year update of cardiac dysfunction in NSABP B-31. The study revealed that the cumulative incidence at 5 years of a class III or class IV cardiac event, in the node positive, HER2 positive breast cancer treated with doxorubicin and cyclophosphamide followed by paclitaxel and one year of trastuzumab was 2.7 percent, compared to 1.3 percent in the non-trastuzumab arm. The 3-year cumulative incidence of cardiac events was 4.1 percent compared to 0.8 percent. Risk factors for women who develop a cardiac event are age greater than 50 years, use of anti-hypertensive medications, and post-doxorubicin ejection fraction of 50-54 percent.

Abstract 512, an update from the combined analysis of NCCTG N9831 and NSABP B-31, continued to show a benefit for the addition of trastuzumab to high-risk HER2 positive breast cancer treated with doxorubicin, cyclophosphamide, and paclitaxel. With a median follow-up of 2.9 years, the 4-year disease-free survival rate and overall survival rate were 85.9 percent and 92.6 percent, respectively, compared to 73 percent and 89 percent in the chemotherapy-alone arm. This benefit persists despite crossover from trastuzumab use. Trastuzumab, despite toxicity, clearly adds to the breast cancer armamentarium. *Abstract 511* revealed that central testing results from NSABP B-31 question the current definition of HER2 overexpression in identifying disease that may benefit from trastuzumab in the adjuvant setting. Benefit was observed in patients with tumors negative by FISH and less than 3+ staining intensity by IHC (relative risk 0.36, p=0.032).

In *Abstract 516,* ECOG 1199 investigated the use of paclitaxel or docetaxel given every 3 weeks or weekly following 4 cycles of doxorubicin and cyclophosphamide. The study demonstrated no difference in disease-free survival when comparing taxane or schedule.

In *Abstract 517,* a Phase III randomized trial compared doxorubicin and cyclophosphamide followed by paclitaxel, with doxorubicin and paclitaxel followed by weekly paclitaxel. At 5 years there was a significant improvement in overall survival in the doxorubicin and paclitaxel followed by weekly paclitaxel arm (89 percent compared to 86 percent, p=0.054).

Breast Cancer: Advanced

Abstract LBA1005 presented the Anglo-Celtic IV trial first results. This UK National Cancer Research Network Phase III trial compared weekly to every 3 week paclitaxel dosing for patients with locally advanced or metastatic breast cancer. Preliminary results show that for matched total dose of paclitaxel, weekly paclitaxel produced a higher response rate, 42 percent compared to 27 percent (p=0.002), respectively.

Abstract 1008 reported on BCIRG 007, presenting survival data from the randomized Phase III trial of trastuzumab plus docetaxel with or without carboplatin in first-line metastatic therapy for breast cancer. Median survival was greater than 36 months and time to progression was greater than 10 months in both arms. There was a trend toward a higher rate of neutropenic infection in the docetaxel and trastuzumab arm (docetaxel at 100 mg/m^2) and a trend toward more thrombocytopenia and anemia in the docetaxel, carboplatin, and trastuzumab arm (docetaxel at 75 mg/m^2). The bottom line appears to be "pick your toxicity."

Abstract 1006 reported on the Phase III trial of capecitabine and ixabepilone compared to capecitabine alone. The study offered exciting results in the heavily pretreated metastatic breast cancer population previously treated with anthracycline and taxanes. Superior efficacy was noted in the combination arm with a progression-free survival hazard ratio (HR) of 0.75, but a greater risk of toxic death for patients with liver dysfunction.

In *Abstract 1032,* 130-nM albumin-bound (*nab*) paclitaxel at 300 mg/m^2 every 3 weeks, 100 mg/m^2 weekly 3 weeks of 4, 150 mg/m^2 weekly 3 weeks of 4, or docetaxel 100 mg/m^2 every 3 weeks was compared for efficacy and toxicity. The response rates of every 3 week therapy were comparable (33 percent for *nab*-paclitaxel and 36 percent for docetaxel). The response rates of weekly *nab*-paclitaxel were greater than every 3 week dosing (58 percent for 100 mg/m^2 and 62 percent for 150 mg/m^2). There was less frequency of NCI CTC grade 4 neutropenia and febrile neutropenia with *nab*-paclitaxel compared to docetaxel.

Abstract 1011 looked at a Phase III double-blinded study comparing paclitaxel to paclitaxel with lapatinib for first-line metastatic breast cancer with HER2 negative or untested HER2 status. No difference was detected in event-free survival or overall survival.

Abstract 1012 summarized a Phase II study of lapatinib as monotherapy in patients having prior treatment with trastuzumab, cranial radiation, and subsequent progressive brain disease demonstrated a 20 percent decrease in disease volume in 16 percent of the 104 enrolled patients.

Prostate Cancer

Abstract 5014 presented results of EORTC trial 22961, comparing 6 months with 3 years of androgen deprivation

therapy (ADT) in conjunction with external beam radiation. Patients with Stage T1c-T2a/b, N1-2 or pN1-2 or T2c-T4, N0-2, M0 were treated with 60-74 Gy of external beam radiation with an LHRH agonist and antiandrogen for 6 months. Patients were then randomized to continue ADT for 30 months or stop ADT. The study was powered to demonstrate a non-inferior overall survival. With a median follow-up of 5.2 years, the overall survival was 85.3 percent compared to 80.6 percent, for 3 years and 6 months of ADT, respectively (p=0.6543 for non-inferiority endpoint, p=0.0191 for 3-year superiority). Based on these results, non-inferiority cannot be confirmed and long-term ADT should remain the standard of care.

For advanced prostate cancer, *Abstract 5015* reported on a randomized study of intermittent compared to continuous androgen suppression. Patients with advanced disease were treated with goserelin and bicalutamide for 24 weeks. Those patients that demonstrated a PSA < 4 mg/dL or a decrease of > 90 percent were randomized to intermittent or continuous therapy. Those on the intermittent arm stopped therapy and resumed when PSA > 10 mg/dL and stopped therapy again when PSA < 4 mg/dL. Those on the continuous arm continued on therapy. Patients on both arms proceeded to second-line therapy when a three-fold rise in PSA was demonstrated. With 335 patients randomized and a median follow-up of 50 months, the primary endpoint of time to progression was reached. By an intention to treat analysis, the intermittent compared to continuous therapy resulted in a median time to progression of 16.6 months and 11.5 months, respectively (p=0.17). These results add to two other randomized controlled studies that support a non-inferiority of intermittent androgen deprivation for advanced prostate cancer.

Colon Cancer: Adjuvant

Abstract 4007 presented the final results of the MOSAIC study with 6 years of follow-up. The MOSAIC study enrolled 2,246 subjects with Stage II or III colon cancer to a regimen of 5FU and leucovorin (LV5FU2) or FOLFOX every 2 weeks for a total of 12 cycles. The primary endpoint of 3-year disease-free survival (DFS) has been published previously and has established FOLFOX as a standard regimen for Stage III colon cancer. With 5 years of follow-up, the difference in disease-free survival was maintained for FOLFOX compared to LV5FU2 (73.3 percent and 67.4 percent, HR of 0.8 and p=0.003). This difference was more pronounced for Stage III colon cancer (HR 0.78, p=0.005) while not statistically significant for Stage II (HR 0.84, p=0.258). This benefit comes at a cost; the peripheral neuropathy related to oxaliplatin can be problematic. The incidence of grade 3 sensory neuropathy continues to decrease from 12.4 percent during therapy to 0.7 percent at 4 years. As predicted, the overall survival (OS) correlates with the disease-free survival. The OS for Stage III colon cancer treated with FOLFOX was 73 percent at 6 years, compared to 68.8 percent for LV5FU2 (HR 0.80, p=0.029). For Stage II colon cancer, no overall survival benefit was evident with FOLFOX compared to LV5FU2 (86.9 percent and 86.8 percent). Based on these findings, FOLFOX provides a significant survival benefit compared to LV5FU2 for patients with Stage III colon cancer but not for Stage II. Until an appropriately powered study is done for Stage II colon cancer, the addition of oxaliplatin cannot be recommended.

Colon Cancer: Advanced

The OPTIMOX 2 study, *Abstract 4013,* evaluated the role of a chemotherapy-free interval during the treatment of advanced colorectal cancer. Originally designed as a Phase III study with a primary endpoint of overall survival, it was downgraded to a large Phase II study when accrual suffered due to the approval of bevacizumab in first-line therapy. Approximately 200 patients were randomized to 6 cycles of FOLFOX followed by either LV5FU2 maintenance or no therapy with resumption of FOLFOX at the time of progression beyond baseline. Maintenance chemotherapy, compared to a chemotherapy-free interval, provided a longer duration of disease control and overall survival (26 months compared to 19 months, p=0.0549). Based on these results, a chemotherapy-free interval after 6 cycles of FOLFOX is not recommended.

Abstract 4012 summarized the CAIRO study that compares sequential single-agent therapy to combination therapy for advanced colorectal cancer. Patients randomized to the sequential arm received capecitabine as first-line therapy, followed by irinotecan at the time of progression, and the combination of capecitabine and oxaliplatin as third-line therapy. Those randomized to the combination chemotherapy arm received the capecitabine and irinotecan combination followed by capecitabine and oxaliplatin at the time of progression. The median overall survival was not statistically different for the sequential and combination therapy arms (16.3 months and 17.4 months, p=0.33). There was an increased response rate for the combination-therapy arm compared to the single agent (41 percent and 20 percent, p<0.0001). Sequential single-agent therapy is an acceptable alternative for the appropriate patient.

Abstract 4000, the CRYSTAL Study evaluated the use of the EGFR inhibitor cetuximab as first-line therapy with FOLFIRI for patients with EGFR expressing colon tumors. The primary endpoint was progression-free survival. The progression-free survival was 8.0 months for FOLFIRI and 8.9 months for FOLFIRI with cetuximab (p=0.0479), a 1-year progression-free survival rate of 23 percent and 34 percent respectively and a response rate of 38.7 percent and 46.9 percent respectively. These findings were more pronounced for patients with liver-only metastases. Similar to findings in other studies, the progression-free survival did correlate with the grade of skin toxicity seen (5.4 months, 9.4 months and 11.3 months for grade 0-1, 2 and 3 skin toxicity, respectively). These results reinforce the importance of clinical trial CALGB 80405 comparing bevacizumab, cetuximab, or both with combination chemotherapy as first-line therapy for metastatic colorectal cancer.

Lung Cancer: Non-small Cell

The lung cancer information most likely to change practice patterns revolves around maintenance chemotherapy, specifically for unresectable Stage III disease, and the timing of additional therapies.

Abstract 7512 presented the HOG LUN 01-24/USO-023 Phase III trial evaluating cisplatin and etoposide with concurrent chest radiation with a subsequent randomization to 3 cycles of docetaxel or observation in patients with Stage III inoperable non-small cell lung cancer. Median survival time was 21.6 months for the docetaxel arm and 24.2 months for the observation arm (p=0.9402). The addition of consolidation docetaxel is significant for an increase in the

rate of hospitalizations and premature death. The authors recommend against the continued use of docetaxel as consolidation in Stage III non-small cell lung cancer.

Abstract 7513 reported on the SWOG study 0023 evaluating maintenance gefitinib after concurrent cisplatin, etoposide, and radiation with consolidation docetaxel. These patients are unselected for EGFR mutations and randomized to gefitinib or observation. The median overall survival from the time of randomization was 23 months for the gefitinib patients compared to 35 months for the observation patients. A pre-emptive strike with gefitinib is not advised outside of a clinical trial setting.

The use of bevacizumab in the elderly population continues to proceed with caution. *Abstract 7535,* an analysis of the elderly cohort from ECOG 4599 of advanced non-small cell lung cancer treated with carboplatin, paclitaxel, and bevacizumab, noted interesting trends. With the addition of bevacizumab, the age group greater than 70 years experienced a trend towards superior response rate (29 percent compared to 17 percent, p= 0.067) and median progression-free survival (5.9 months compared to 4.9 months, p= 0.063), although there was no difference in overall survival (11.3 months compared to 12.1 months, p= 0.4). Hypertension, bleeding, and proteinuria were more common in the elderly. Treatment related deaths were more common in the bevacizumab arm than in the chemotherapy-alone arm (6.3 percent and 1.8 percent, respectively). In the elderly, the data hint toward more toxicity, possibly with less gains, however additional data continue to support the benefits of bevacizumb in Stage IV lung cancer patients who meet appropriate criteria.

Abstract LBA7514 looked at a randomized Phase III trial comparing cisplatin and gemcitabine with placebo to bevacizumab at 7.5 mg/kg or 15 mg/kg every 3 weeks. The primary endpoint of progression-free survival was improved with the addition of bevacizumab at both doses, with HR of 0.75 (p=0.002) and 0.82 (p=0.03), respectively. No unexpected toxicities were detected. The data were consistent with the carboplatin, paclitaxel, and bevacizumab results from ECOG 4599.

Lung Cancer: Small Cell

The role of prophylactic cranial irradiation for small cell lung cancer has been controversial. Data supporting prophylactic cranial irradiation in limited-stage small cell lung cancer has matured and demonstrates a survival benefit. *Abstract 4* looked at the EORTC 08993-22993 study that expands the cohort to include extensive-stage small cell lung cancer. Patients with extensive-stage small cell lung carcinoma who were responding to initial chemotherapy were randomized to whole brain radiation (doses ranging from 20 Gy in 5 fractions to 30 Gy in 12 fractions) or observation. The primary endpoint was the cumulative incidence of symptomatic brain metastases. Imaging of the brain was performed whenever any of the pre-defined "key-symptoms" were present at baseline or during follow-up. The 1-year cumulative incidence of symptomatic brain metastases was 14.6 percent with radiation versus 40.4 percent for controls, with non-overlapping confidence intervals (CI). Radiation significantly prolongs progression-free survival time (p=0.0218, HR=0.76, CI: 0.59-0.96) and overall survival (p=0.0033, HR=0.68, CI: 0.52-0.88). The 1-year survival rate was 27.1 percent for the radiation and 13.3 percent for the control arm. Prophylactic cranial irradiation should be offered to patients with extensive-stage disease demonstrating a response to initial chemotherapy.

Hematologic Malignancy

Abstract 2 presented a randomized Phase III study designed to evaluate the benefit and toxicity of As_2O_3 as first post-remission therapy for newly diagnosed patients with acute promyelocytic leukemia (APL). Adult patients were randomized to receive 2 courses of As_2O_3 (0.15 mg/kg/d for 5 days each week for 5 weeks) as a first consolidation if they achieve remission after induction with oral tretinoin, daunorubicin, and cytarabine. Subsequent consolidation on both arms includes 2 courses of tretinoin and daunorubicin. Event-free survival, the primary endpoint, was 77 percent at 3 years on the As_2O_3 arm (median, not reached) compared to 59 percent at 3 years on the standard arm (median of 63 months, p=0.0013). Overall survival was 86 percent at 3 years on the As_2O_3 arm compared to 77 percent at 3 years on the standard arm (medians not reached, p=0.029). The addition of 2 courses of As_2O_3 consolidation therapy following remission induction significantly improves survival.

Abstract *LBA8025* reported on a Phase III trial evaluating lenalidomide with high- versus low-dose dexamethasone for newly diagnosed multiple myeloma. Major grade 3 or higher toxicities with high- versus low-dose dexamethasone include thromboembolism (22.1 percent compared to 6.1 percent), infection/pneumonia (15.7 percent compared to 7.5 percent), and hyperglycemia (9.7 percent compared to 6.6 percent). Overall survival at first interim analysis was significantly superior with low-dose dexamethasone (1 year survival of 96.5 percent compared to 86 percent, p<0.001). The data monitoring committee recommended release of survival results, switching all patients to lenalidomide with low-dose dexamethasone, and closure of an expansion-Phase trial of lenalidomide with high-dose dexamethasone investigating optimal thromboprophylaxis.

Head and Neck Cancer

The focus of the head and neck presentations was the benefit, schedule, and use of the epidermal growth factor inhibitors and possible therapeutic changes ahead for I-131 thyroid cancer failures.

Squamous Cell Carcinoma

Abstract 6091 looked at the randomized Phase III Extreme study that compares a maximum of 6 three-weekly cycles of cisplatin (100 mg/m² IV on day 1) or carboplatin (AUC 5, day 1) and 5-FU (1000 mg/m²/day continuous infusion for the first 4 days of each cycle) with or without cetuximab delivered until progression or unacceptable toxicity for first-line therapy in recurrent or metastatic squamous cell cancer. The median survival was 7.4 months in the chemotherapy-alone arm compared to 10.1 months for chemotherapy with cetuximab (p=0.036).

Abstract 6013 revealed the final results of a Phase II trial using erlotinib, docetaxel, and cisplatin in recurrent metastatic squamous cell carcinoma reporting a median survival of 11 months and progression-free survival of 6 months. Toxicities of diarrhea, rash, and nausea were common. Correlative markers including downstream EGFR pathway markers (p-akt, mek, k-ras) are being analyzed.

Abstract 6015 reported on a Phase II study of con-

current therapy with induction cetuximab (250 mg/m^2), carboplatin (AUC of 2), and paclitaxel (90 mg/m^2) weekly for Stage III/IV operable squamous cell carcinomas of the head and neck. Restaging primary-site biopsy was done at week 8 if there was a clinical response. Patients with a negative biopsy had completion radiation (68-72 Gy) with weekly chemobiotherapy. Patients with a positive biopsy (or persistent tumor) had a restaging biopsy at week 14 after chemobioradiation (50 Gy). If primary-site biopsy was negative, patients had completion radiation (68-72 Gy) with chemobiotherapy. If primary-site biopsy was positive at 14 weeks, salvage surgery was required. A high induction response rate with complete pathologic response in 40 patients (65 percent) at week 8 and the remaining 28 (100 percent) at week 14 after concurrent chemobiotherapy and radiation was reported. Further studies are warranted and long-term survival data are awaited.

Thyroid Cancer

Abstract 6008 looked at a Phase II study of axitinib, a small molecule inhibitor of VEGF receptors 1, 2, and 3, in metastatic or unresectable thyroid cancers refractory or not suitable for iodine therapy. The oral agent was administered twice daily with expected toxicities of proteinuria, fatigue, hypertension, diarrhea, and mucositis. The investigator-reported best response was: partial for 30 percent, stable for 42 percent, progression for 12 percent, and indeterminate or unknown for 17 percent. Progression-free survival was 18.6 months at median follow-up of 273 days. A global pivotal trial of axitinib in doxorubicin refractory thyroid cancer is ongoing.

Pancreas Cancer

The results of two randomized Phase III studies were reported. *Abstract 4508* presented the CALGB 80303 study comparing standard dose gemcitabine with placebo or bevacizumab at 10 mg/kg. With 540 patients with advanced pancreas cancer randomized, there was no difference in response rate, overall survival (6.1 months and 5.8 months, respectively), or 1-year survival (20 percent and 18 percent, respectively). Correlative studies, including pharmacogenomics, quality of life, and angiogenesis biomarkers, are still to be reported. *Abstract 4509* looked at the SWOG 0205 study that compared single-agent gemcitabine to gemcitabine with cetuximab based on results of Phase II studies. EGFR staining was not required for eligibility. With 735 patients randomized, there was no statistically significant difference in response rate or overall survival (5.9 months and 6.4 months, respectively, p=0.14). Further research is needed to better define the role of EGFR inhibition for advanced pancreas cancer in light of the statistically significant (but clinically questionable) benefit of erlotinib previously demonstrated.

Renal Cell Cancer

Abstract 3 presented the interim analysis of AVOREN, a randomized Phase III study comparing IFN-α2a with or without bevacizumab for advanced renal cell cancer (RCC). There were 649 patients with metastatic RCC after nephrectomy randomized to receive IFN-α2a 9 million units 3 times weekly with either bevacizumab 10 mg/kg every 2 weeks or placebo. The study was powered to detect an improvement in overall survival from 13 months to 17 months. The addition of bevacizumab compared to placebo improved response rate (31 percent and 13 percent, respectively p=<0.0001), progression-free survival (10.2 months and 5.4 months, respectively, p< 0.0001), and overall survival (HR=0.75 with a 95 percent; CI: 0.58-0.97, median overall survival not yet reached for bevacizumab arm). Increased grade 3 and 4 adverse events were seen in the bevacizumab arm and include: fatigue (23 percent compared to 15 percent), proteinuria (6.5 percent compared to 0), hypertension (3.9 percent compared to 0.7 percent), hemorrhage (3.3 percent compared to 0.3 percent), venous thrombosis (1.8 percent compared to 0.7 percent), gastrointestinal perforation (1.5 percent compared to 0), and arterial ischemia (1.2 percent compared to 0.3 percent). The preliminary results of the similarly designed CALGB study should be available soon and provide important information that will either confirm or refute these data.

Two other first-line studies for advanced RCC were presented. *Abstract 5024* presented the updated results of sunitinib compared to IFN-α along with the analysis of prognostic factors. With 375 subjects in each arm, sunitinib demonstrated a superior response rate (44 percent compared to 11 percent, p <0.000001), median duration of response (12 months compared to 10 months), and median progression-free survival (11 months compared to 4 months). The sunitinib benefit in progression-free survival extended across all Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic-risk-factor groups (HR=0.488; 95 percent; CI: 0.406-0.586). *Abstract 5025* reviewed a randomized Phase II study comparing sorafenib to IFN-α with a primary endpoint of progression-free survival. For the study 189 patients with advanced RCC were randomized to sorafenib 400 mg twice daily with the option to dose escalate to 600 mg twice daily at the time of progression or IFN-α 9 mu three times weekly and an allowance to cross over to sorafenib at the time of progression. For sorafenib compared to IFN-α, the median progression-free survival was 5.7 months (CI: 5.0-7.4 months) and 5.6 months (CI: 3.7-7.4 months), respectively; a total of 11 percent and 15 percent, respectively, discontinued due to adverse events. Skin toxicity (rash and hand-foot skin reaction) and diarrhea occurred more frequently in the sorafenib group, and flu-like syndrome occurred more frequently in the IFN-α group. The median progression-free survival was 5.3 months (CI: 3.6-6.1 months) in patients (n=50) who crossed from IFN-α to sorafenib and 3.6 months (CI: 1.9-5.3 months) for patients (n=44) with dose escalation to 600 mg twice daily of sorafenib. The primary endpoint was not met for this first-line therapy study, but activity was demonstrated and increased dosage is worthy of further exploration.

Abstract 5023 presented the final overall survival results of the randomized Phase III study of sorafenib compared to placebo for advanced RCC after failure of one prior therapy. The preliminary results of progression-free survival were previously presented and as a result the study was unblinded and the patients randomized to the placebo were crossed over to receive sorafenib. The overall survival analysis before crossover showed an estimated 39 percent overall survival improvement for sorafenib compared to placebo (HR=0.72, p=0.018). Two hundred and sixteen patients on placebo crossed to sorafenib. The overall survival 6 months after crossover show a 30 percent improvement with sorafenib (HR=0.77, p=0.015). The final overall survival showed an improvement of 13.5 percent for sorafenib compared to placebo and was not significant (median 17.8 compared to 15.2

months; HR=0.88, p=0.146; a=0.037). Secondary analysis censoring placebo data showed a significant overall survival benefit for sorafenib compared to placebo (HR=0.78, 95 percent; CI: 0.62-0.97; p=0.0287; a=0.037), suggesting crossover has confounded overall survival. Over 700 patients have correlative biomarker analysis. Using a COX proportional hazards model, baseline VEGF is an independent prognostic factor (p=0.014); patients with high baseline VEGF (>131 pg/ml) have poorer prognosis and a trend towards greater progression-free survival benefit with sorafenib compared to placebo (HR=0.48 compared to 0.64 for high compared to low VEGF, p=0.096).

Hepatocellular Cancer

Abstract LBA1 looked at the multitargeted tyrosine kinase inhibitor sorafenib in a Phase III randomized trial for patients with advanced hepatocellular cancer (HCC). Patients with histologically proven HCC, Child-Pugh score A cirrhosis, and ECOG PS of 0-2 were randomized to placebo or sorafenib at 400 mg twice daily. Therapy was generally well tolerated with an increased incidence of grade 3 or 4 diarrhea (8 percent), anorexia, erythrodysesthesia (8 percent), and alopecia. For those patients receiving sorafenib compared to placebo the response rate is 2.3 percent (no complete responses) and 0.7 percent, respectively, and the 4-month progression-free rate was 62 percent and 42 percent, respectively. The overall survival was 10.7 months compared to 7.9 months, respectively, (HR=0.69, 95 percent; CI: 0.55-0.88; p=0.00058). The time to progression was prolonged from 12.3 weeks with placebo to 24.0 weeks with sorafenib (p=0.000007). While this is certainly a positive study and sorafenib demonstrates a statistically significant improvement in survival, the population studied is a select population. HCC has a distinct geographic variation. The majority of the patients in this study were enrolled from a European center (88 percent), less than 50 percent with viral hepatitis, 26 percent with alcoholic cirrhosis, and 92 percent with ECOG PS 0-1. The benefit of sorafenib for patients with compromised liver function is uncertain.

Melanoma: Adjuvant

Abstract 8504 presented the final results of EORTC 18991 comparing PEG-IFN (induction and maintenance for up to 5 years) to observation for high-risk melanoma, stratified for nodal involvement. Relapse-free survival favors PEG-IFN with a median of 34.8 months compared to 25.5 months (HR 0.82, p=0.011). Distant-metastases-free survival was not significantly different (HR 0.88, p=0.107) nor was overall survival (HR 0.98, p=0.78). Patients with microscopic-only nodal disease (N1) had a greater benefit from PEG-IFN compared to those with N2 disease. The HR for relapse-free survival, distant-metastases-free survival, and overall survival for N1 disease was 0.73 (p=0.02), 0.75 (p=0.03) and 0.88 (p=0.43); and for N2 disease was 0.86 (p=0.12), 0.94 (p=0.53) and 1.01 (p=0.91). This trend of increased benefit in lower-disease-burden patients has also been noted in EORTC 18952.

Abstract 8505 looked at data from ECOG 1684, a randomized Phase III adjuvant study comparing high-dose IFN-α2b therapy for 4 weeks to the same therapy with maintenance subcutaneous interferon continued for 48 weeks for Stage IIB-III resected melanoma. The study was presented as a non-inferiority trial. At a median follow-up of 51 months, there was no difference in overall survival (61 months and 63 months, respectively, p=0.444) or disease-free survival (32 months and 31 months, respectively, p=0.836) in the two groups. The shorter duration of therapy was associated with better tolerance and a higher patient compliance rate. ECOG 1697, a Phase III trial comparing high-dose interferon for 4 weeks to observation, is currently underway and those results are anxiously awaited.

Melanoma: Metastatic

Abstract 8510 reported on a Phase III study of carboplatin and paclitaxel with sorafenib or placebo as second-line therapy in metastatic melanoma. Patients with progressive disease on dacarbazine or temozolomide-containing regimens, with prior immunotherapy allowed, were enrolled. The study was powered to detect a HR of 0.56 with a primary endpoint of progression-free survival. The primary endpoint was not met with a median progression-free survival of 17.4 weeks for sorafenib and 17.9 weeks for placebo (HR=0.906, p=0.492). No improvement in survival or response rate was noted with the addition of sorafenib. The ongoing ECOG 2603 study is evaluating this regimen in chemotherapy naïve patients.

Abstract 8511 presented a look at a randomized Phase II study evaluating dacarbazine with placebo or sorafenib for chemo-naive patients with metastatic melanoma. The median progression-free survival was 11.7 weeks and 21.1 weeks (HR=0.67, p=0.07), respectively. The rate of grade 3 toxicities were greater with sorafenib compared to placebo respectively, including neutropenia (33 percent and 12 percent), leukopenia (14 percent and 6 percent), thrombocytopenia (35 percent and 18 percent), thrombosis/embolism (6 percent and 0 percent), hypertension (8 percent and 0), hand-foot skin reaction (4 percent and 0), and CNS hemorrhage (8 percent and 0 percent). This regimen warrants further evaluation in larger clinical trial settings.

Supportive Care

With the increased use of epidermal growth factor inhibitors, comes the new skin toxicity, the 'acneiform' rash. *Abstract 9006* reported on the N03CB study that randomized 61 patients within 7 days of receiving an EGFR inhibitor without a demonstrable rash to receive tetracycline or placebo. Rash was assessed by monthly physician reports using the Common Terminology Criteria version 3 (primary endpoint) and weekly patient reports. No difference was reported for tetracycline or placebo in the incidence of rash: 70 percent and 76 percent respectively at 4 weeks, and 87 percent and 84 percent respectively at 8 weeks. A benefit is suggested in severity of rash grade 2 or greater with tetracycline compared to placebo: 17 percent and 55 percent respectively at 4 weeks (p=0.009) and 27 percent and 47 percent respectively at 8 weeks (p=0.3). Patient reported results were similar to physician reported results. Diminished rash severity and improved quality of life suggest a role and need for further study of this antibiotic.

Ann L. Mellott, MD, is a medical oncologist with Hematology Oncology Associates of Illinois at Northwestern University, and Mary F. Mulcahy, MD, is a medical oncologist with the Northwestern Medical Faculty Foundation at Northwestern University in Chicago, Ill.