MEETING HIGHLIGHTS

European Society for Medical Oncology

and

Association for the Study of Bone and Mineral Research

Walter Alexander

European Society for Medical Oncology

Identifying Benefited Subgroups and Promising Agents

Cetuximab (Erbitux) for Colorectal Cancer

• Christos Karapetis, MD, Flinders University, Adelaide, Australia

The presence of K-ras mutations provides a strong argument against the use of cetuximab (Erbitux, Bristol-Myers Squibb) in pretreated metastatic colorectal cancer, according to results of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG CO.17), presented as a late-breaking clinical trial by Dr. Karapetis. The K-ras gene plays an important role in cell-growth regulation and oncogenesis. Although anti-epidermal growth factor receptor (EGFR) therapies such as cetuximab block receptor activation, mutated K-ras genes remain “turned on” regardless of receptor inhibition, Dr. Karapetis said, suggesting a potential negative predictive value.

Dr. Karapetis and colleagues looked at samples from 394 patients enrolled in the cetuximab phase 3 Eastern Cooperative Oncology Group (ECOG 0-2) trial who had been randomly assigned to receive, in a 1:1 ratio, intravenous (IV) cetuximab (400 mg/m² in week 1, then 250 mg/m² IV weekly) plus best supportive care (BSC) or BSC alone. Treatment was continued until disease progression or until unacceptable toxicity occurred. The primary endpoint was overall survival.

For the secondary endpoint of progression-free survival, analysis showed identical median progression-free survival of 1.8 months for the two treatment groups among those with mutated K-ras genes. Among patients with the wild-type K-ras gene, however, progression-free survival was nearly doubled in the cetuximab/BSC group at 3.8 months, compared with 1.8 months in the BSC-alone group ($P < 0.0001$).

For the primary endpoint of overall survival, again among patients with mutated K-ras genes, findings were similar: 4.5 months for cetuximab plus BSC and 4.6 months for BSC alone ($P = 0.89$). For wild-type K-ras, there was a significant advantage in survival when cetuximab was added, as follows: cetuximab plus BSC, 9.5 months; BSC alone, 4.8 months ($P < 0.0001$).

Dr. Karapetis concluded: “K-ras is a marker that predicts who will benefit from cetuximab, and cetuximab does provide survival advantage, but only if the tumor has the wild-type K-ras.”

Pazopanib in Non–Small-Cell Lung Cancer

• Nasser Altorki, MD, Professor, Cardiothoracic Surgery, and Director, Division of Thoracic Surgery, New York Presbyterian–Weill Cornell Medical Center, New York, N.Y.

• Jose Baselga, MD, Chief, Medical Oncology Service, Vall d’Hebron University Hospital and Céntro Medico Teknon, Barcelona, Spain

A small early-phase trial of an investigative agent, pazopanib (GlaxoSmithKline), was selected for inclusion in the opening ESMO press conference because of the drug’s impressive single-agent activity with short-term treatment in early stage non–small-cell lung cancer (NSCLC). Pazopanib is an oral angiogenesis inhibitor and targets vascular EGFR (VEGFR), platelet-derived growth factor receptor (PDGFR), and c-kit.

The study, stated lead investigator Dr. Altorki, enrolled 35 subjects with stage 1A-1B (33 patients, 94%) or stage 2A-2B NSCLC (two patients, 6%). The patients had received no cytotoxic, anti-angiogenic, or investigative therapy in the previous six months. The primary objective was to evaluate reductions in tumor volume after pazopanib treatment, as measured by high-resolution computed tomography.

Each subject received pazopanib 800 mg preoperatively once daily for two to six weeks, followed by CT scanning and blood plasma evaluation. Surgical resection and biopsy followed. Reporting on the primary endpoint, Dr. Altorki said that after a median of 16 days of treatment, 30 patients (85.7%)...
achieved a reduced tumor volume. The safety profile, he said, was acceptable. He added:

The most important finding is that you can give the drug to patients with early-stage disease. It is safe, well tolerated, and it does not in any way change or alter their suitability for surgery. The final, remarkable and unexpected result was that 30 out of 35 patients in the study had tumor shrinkage despite the short-term nature of the treatment.

“This is a phenomenally innovative study,” said Dr. Baselga, briefing moderator and president of ESMO. “This research could really facilitate the work of surgeons and could help increase cure rates.”

**Everolimus (Certican) for Pancreatic Tumors**
- James C. Yao, MD, MD Anderson Cancer Center, Houston, Tex.

In a study led by Dr. Yao, everolimus (RAD001, Certican, Novartis), a derivative of sirolimus (Rapamycin, Wyeth), when combined with octreotide acetate (Sandostatin LAR Depot, Novartis), a somatostatin analogue (and the standard treatment for controlling symptoms of refractory pancreatic neuroendocrine tumors), yielded more than double the progression-free survival of historical treatment. RAD001 is an oral inhibitor of the mammalian target of rapamycin (mTOR) with broad antitumor activity.

In Dr. Yao’s phase 2 study, 115 patients were randomly assigned to receive RAD001 alone at a dose of 10 mg/day and 45 patients received RAD001 10 mg/day plus Sandostatin LAR at a dose of 30 mg or less every 28 days. The primary endpoint of the study was the objective response rate; secondary endpoints included duration of response, safety, progression-free survival, and survival.

Treatment was well tolerated. The most common grade 3 adverse events thought to be related to treatment were asthenia, fatigue, and thrombocytopenia. Five patients in the RAD001 group and four patients in the combination group discontinued therapy because of adverse events.

The median age was 55 years in both groups. By central review, objective response rates (according to RECIST, a standard measure of tumor response) were 7.8% for RAD001 and 4.4% for RAD001/Sandostatin LAR. All responses were partial. Investigator assessment, however, placed the objective response rate at 7% for RAD001 and at 8.9% for RAD001/Sandostatin LAR.

Stable disease rates, as measured by central review, were 68.7% for RAD001 and 77.8% for RAD001/Sandostatin LAR; these rates, as assessed by the investigators, were 66.1% for RAD001 and 71.1% for the combination, respectively. Clinical benefit rates (partial response plus stable disease) were 76.5% and 82.2% by central review and 73% and 80% by investigator assessment, respectively.

Showing the clearest advantage for RAD001/Sandostatin LAR, progressive disease rates by central review were 13.9% for RAD001 alone and 2.2% for the combination. By investigator review, they were 18.3% for RAD001 alone and 11.1% for the combination. Median duration of response for RAD001 was 10.6 months by central review and 10.15 months by investigator assessment and had not been reached in the combination group.

At six months, progression-free survival by central review was 9.3 months for RAD001 and 12.9 months for RAD001/Sandostatin LAR. Median overall survival had not been reached in either group.

Dr. Yao characterized the risk–benefit ratio as positive. He stated that with RAD001 being active as both monotherapy and in combination with Sandostatin LAR in refractory pancreatic neuroendocrine tumors, further investigation is warranted.

**Lapatinib (Tykerb) for Squamous Cell Head and Neck Cancer**
- Maria Del Campo, MD, Department of Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain

In another trial of an investigative agent in advanced disease, Dr. Del Campo reported promising findings for the tyrosine kinase inhibitor lapatinib (Tykerb, GlaxoSmithKline) in advanced squamous cell carcinoma (SCC) of the head and neck.

“Lapatinib improved response to chemoradiation,” Dr. Del Campo said.

In the phase 2 randomized trial, investigators assigned 107 therapy-naïve patients with locally advanced head and neck cancer to receive oral lapatinib 1,500 mg or placebo for two to six weeks, followed by standard treatment with concurrent platinum-based chemotherapy and radiation. Subjects were followed for 12 weeks after they completed chemoradiation.

Dr. Del Campo reported that treatment was well tolerated. There was a modest but statistically significant reduction in mean tumor cell proliferation in the lapatinib patients (~8%) compared with the placebo patients (~2.7%) (P = 0.039). In the subset of 40 patients who underwent radiological scanning after lapatinib monotherapy, 17% achieved complete or partial responses, compared with none of the patients in the placebo arm.

Among 88 patients evaluable for radiological analysis after completing chemoradiation, 86% of lapatinib-treated subjects and 63% of placebo subjects achieved complete and partial responses. Response rates following chemoradiation differed between the two groups: 28% of lapatinib patients achieved complete responses, compared with 7% of placebo patients. The results suggested that lapatinib might be enhancing the therapeutic effects of subsequent chemoradiation.

Dr. Del Campo concluded that lapatinib alone showed encouraging activity. Phase 3 studies of lapatinib for head and neck cancer are now recruiting patients, she said.

**Antibody CP-751871 for Non–Small-Cell Lung Cancer**
- Luis Paz-Ares, MD, PhD, Chief, Division of Medical Oncology, Virgen del Rocío University Hospital, Seville, Spain

Compared with chemotherapy (paclitaxel plus carboplatin) alone, Pfizer’s insulin-like growth factor type-I receptor (IGF-IR) antibody CP-751871 improved response rates in patients with NSCLC. The greatest benefit was seen in patients with the squamous cell subtype.
Dr. Paz-Ares reported results of a multicenter study among 150 patients with advanced NSCLC. Patients had been randomly assigned, in a 2:1 ratio, to receive chemotherapy plus CP-751871 or chemotherapy alone. Chemotherapy was given as paclitaxel (Taxol, Bristol-Myers Squibb) at a dose of 200 mg/m² plus carboplatin (Paraplatin, Bristol-Myers Squibb), with an area-under-the-curve (AUC) concentration of 6, plus CP-751871 at a dose of 10 mg/kg or 20 mg/kg. Enrolled patients had stage IIIB disease with malignant pleural effusion, stage IV disease, or measurable recurrent disease. Approximately 80% of patients (n = 120) had adenocarcinoma, and 20% (n = 30) had SCC.

In both groups, chemotherapy was given every three weeks for up to six cycles. CP-751871 was given until disease progression. Patients with disease progression in the chemotherapy arm were eligible to receive the antibody alone or the combination.

A post-study extension was conducted among the 30 patients with SCC. The primary endpoint was the objective response rate. Objective response rates were 54% with combination therapy and 41% with chemotherapy alone. In the SCC subpopulation, a dose response was noted for CP-751871, with objective response rates of 78% with 20 mg, 57% with 10 mg, and 46% with chemotherapy alone. The objective response rate for patients receiving CP-751871 alone was 78%.

Among patients with adenocarcinoma, objective response rates were 57% with 20 mg, 38% with CP-751871, and 25% with chemotherapy alone. In patients with undifferentiated tumors, there was no benefit from CP-751871.

“That’s consistent with the minimal IGF-1R expression seen in undifferentiated tumors,” Dr. Paz-Ares said.

Progression-free survival improved, especially in those patients with SCC at the higher CP-751871 dose. Side effects were generally manageable, with grade 3 and 4 fatigue being the most common event in 10% of patients, hyperglycemia occurring in 20%, and neutropenia affecting 30%.

Dr. Paz-Ares concluded that CP-751871 plus chemotherapy improved objective response rates better than chemotherapy alone. He underscored that robust responses, rarely observed with chemotherapy alone, were noted in patients with bulky squamous tumors.

Phase 3 studies in refractory NSCLC are in progress.

Elesclomol in Melanoma

- Steven O’Day, MD, Chief of Research, and Director, Melanoma Program, Angeles Clinic and Research Institute, Santa Monica, Calif.

An investigative injectable agent that increases oxidative stress in cancer cells and leads to apoptosis—Elesclomol (STA-4783, Synta/GlaxoSmithKline)—was found to improve overall survival in patients with metastatic melanoma who received chemotherapy with paclitaxel.

“This novel therapeutic approach,” stated Dr. O’Day, “may make melanoma, a largely chemoresistant disease, more sensitive to chemotherapy.”

Noting that advanced metastatic melanoma is notoriously hard to treat, Dr. O’Day stated that the elesclomol/paclitaxel combination was tolerable in his study, with safety similar to that of paclitaxel alone. Neutropenia, back pain, fatigue, and neuropathy were the most common treatment-related effects.

The study, a two-year follow-up of a randomized phase 2B trial of patients with stage IV metastatic melanoma, compared overall survival for elesclomol at a dose of 213 mg/m² co-infused with paclitaxel at a dose of 80 mg/m² in 53 patients against paclitaxel alone at a dose of 80 mg/m² in 29 patients. Four-week cycles (three weeks of treatment and one week of rest) were administered until disease progression. Participants had received chemotherapy only one time or not at all. Crossing over to dual therapy was allowed for patients whose disease progressed with monotherapy.

Patients receiving elesclomol plus paclitaxel lived an average of four months longer (11.9 months) than patients receiving paclitaxel monotherapy (7.8 months). Two-year survival was also higher in the elesclomol/paclitaxel patients (27%) than for the placebo patients (21%). Among the 68% of paclitaxel patients who crossed over to dual therapy at time of progression, median survival was higher among these patients (14.3 months) than among patients continuing monotherapy after disease progression (5.6 months).

Dr. O’Day concluded that treatment of metastatic melanoma with elesclomol plus paclitaxel led to improved overall survival compared with paclitaxel alone. Phase 3 studies are ongoing.

MEETING HIGHLIGHTS: ESMO and ASBMR

Association for the Study of Bone and Mineral Research

Agents Producing Strong Increases in Bone Density

- Steven Cummings, MD, University of California, San Francisco, Calif.

Denosumab (AMG-162, Amgen) is a fully human monoclonal antibody to RANKL (receptor activator for nuclear factor B ligand), which activates the osteoclast cells involved in breaking down bone. The FREEDOM Trial (Fracture REDuction Evaluation of Denosumab in Osteoporosis every Six Months) enrolled 7,868 postmenopausal women (mean age, 64) from 214 centers in 32 countries. All patients had lumbar

Denosumab: Improving Bone Density
spine or total hip T-scores of between –2.8 and –4, and 23% had prior fractures. Women were randomly assigned to receive subcutaneous (SQ) injections of denosumab 60 mg every six months or placebo. All patients were also taking 400 International Units (IU) of oral vitamin D and 1 g of elemental calcium daily.

After 36 months, women receiving denosumab had a 68% decreased incidence of new vertebral fractures, as confirmed by radiography, compared with women receiving placebo. The reduction was 61% in the first year, increasing to 78% in the second year, and leveling off to 75% in the third year. The incidence of fractures with placebo was 7.2%; with denosumab, the fracture incidence was reduced to 2.3%.

After three years, nonvertebral fractures were also reduced by 20% in the denosumab group, compared with the placebo group. Hip fractures were decreased by 40%.

Dr. Cummings pointed out that the reduced fracture incidence correlated with robust increases in bone mineral density (BMD), including a 9.2% increase in BMD at the lumbar spine and a 6% increase in the hip. Lower fracture risk was also correlated with reductions in biochemical markers of bone turnover, most notably a 72% reduction in serum C-terminal telopeptide after three years.

“Given the strength of the effects on bone density and resorption, I expected to see a strong decrease in fractures. It was what I expected and hoped for,” Dr. Cummings said.

Dr. Cummings also noted a statistically significant reduction in self-reported falls among the denosumab-treated patients. He acknowledged, however, that such reports are difficult to interpret because patients may be more likely to record and report a fall if there was a consequent fracture.

Adverse events were generally similar with denosumab and placebo. Roughly 25% of patients in both groups reported serious adverse effects, with infections at a rate of just over 50% in both groups. Life-threatening adverse events (stroke, cardiac events, atrial fibrillation, and malignancy) were rare in both groups (range, 1%–2%).

Dr. Cummings concluded that twice-yearly injections of denosumab 60 mg resulted in major reductions in the incidence of fractures in this high-risk population.

**Odanacatib: Building New Bone**

- Michael McClung, MD, Director, Oregon Osteoporosis Center, Portland, Ore.

Odanacatib (MK-0822, Merck) is a first-in-class selective inhibitor of cathepsin-K, an enzyme that plays a key role in osteoclastic degradation of the protein content of bone. In a multicenter study involving 399 postmenopausal women with a baseline BMD in the range of –2.0 to –3.5, odanacatib produced dose-dependent increases in BMD.

The women were treated for two years with weekly oral odanacatib at doses of 3, 10, 25, or 50 mg. They also took 5,600 IU of supplemental vitamin D each week. Subjects with an average daily calcium intake under 1,000 mg were also given calcium carbonate 500 mg/day.

At doses of 10, 25, and 50 mg, weekly odanacatib produced significant increases in lumbar, total hip, and femoral neck BMD. Not surprisingly, the 50-mg dose showed the greatest efficacy in building BMD.

At 24 months, patients taking the 50-mg dose showed a mean increase in BMD of 5.48% over baseline at the lumbar spine. Women receiving placebo showed a 0.19% decrease in BMD.

Total hip BMD increased by 3.16%, compared with –0.93% for placebo. Femoral neck BMD increased by 3.84%, compared with –0.85% for placebo. Decreases in BMD were noted at all three sites with the lowest dose of odanacatib (3 mg).

The 50-mg weekly odanacatib dose resulted in a mean 51% decrease in urinary N-telopeptide (uNTx), and a 30.6% reduction in serum C-telopeptide (sCTx), two key markers of bone resorption. In the placebo-treated patients, sCTx increased by 32.8%; Ntx decreased, but only by 4.6%. However, odanacatib 50 mg did produce 13% to 20% increases in markers of new bone formation—in bone-specific alkaline phosphatase (s-BASP) and in serum N-terminal propeptides of type-1 collagen (sP1NP).

Rates of adverse events with odanacatib were similar to those with placebo, with 35% of the women treated with 50 mg reporting adverse effects versus 39.8% of those receiving placebo. Discontinuation rates were 7.7% for those receiving odanacatib 50 mg and 4.8% for those receiving placebo. Nausea, rash, headache, and muscle spasms were the most common odanacatib-associated adverse events.

Dr. McClung mentioned that a large global phase 3 trial is under way to determine whether the changes in BMD and bone turnover found with odanacatib will translate into a reduced incidence of fractures.