Novel Drugs—Miscellaneous Category

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A wide variety of presentations in this session covered a number of drugs that do not "neatly" fit in one or the other sessions at this annual targeted therapy meeting. Dr. Mark Green presented data on bendamustine, a novel alkylating agent and benzimidazole antimetabolite with significant activity in lymphoproliferative disorders. In untreated, extensive stage small cell lung cancer (SCLC), bendamustine had 40% response rate (RR) as a single agent and 73% when combined with carboplatin. Grades 3 to 4 leukopenia (46%) was the most common toxicity. Ongoing SCLC trials evaluate bendamustine with frontline irinotecan and as a single agent in the second line.

Dr. David Ettinger presented data on amrubicin, a synthetic anthracycline that has been extensively evaluated in SCLC. RR more than 20% was seen in a phase II study of patients with platinum refractory SCLC. Clinical evaluation of this agent is ongoing including a phase III trial of cisplatin and amrubicin versus cisplatin and etoposide.

Pralatrexate, FDA approved for treatment of peripheral T-cell lymphoma, is a novel antifolate. Pralatrexate is transported into cells by reduced folate carrier (RFC) and inhibits dihydrofolate reductase. Activity seems independent of thymidylate synthase expression, a potential mechanism of pemetrexed resistance. Dr. Mark Kris outlined multiple trials at Memorial Sloan Kettering evaluating pralatrexate, including a phase I trial in 35 patients with non-small cell lung cancer (NSCLC) with two complete responses and RR of 8%. He outlined a randomized phase II trial of pralatrexate versus erlotinib after platinum-based therapy in current or former smokers.

Dr. Grace Dy presented a detailed evaluation of RFC-1, the primary mechanism of pralatrexate transport into cells. RFC expression is reduced with folate deprivation, and polymorphisms in RFC-1 may be related to response to antifolate therapies. Decreased drug transport into cells by RFC-1 is a mechanism of methotrexate resistance, which may be overcome by pralatrexate given higher affinity for the transporter.

Dr. Everett Vokes presented data on picoplatin, a novel platinum compound designed to overcome platinum resistance. It has a favorable toxicity profile with respect to neurotoxicity and neuropathy, but myelotoxicity is seen. In a phase II study of platinum refractory SCLC (progression 0–180 days after platinum-based therapy), survival compared favorably with historical controls (26 weeks). In the Study of Picoplatin Efficacy After Relapse (SPEAR) trial, picoplatin is compared with best supportive care in the second line after progression on platinum agent, and data should be presented at the American Society of Clinical Oncology (ASCO) 2010.

Dr. Glen Weiss presented data on TH-302, a novel delivery system of a novel hypoxia activated cytotoxic agent. The compound is an alkylator, bromo-isophosphoramide mustard that is activated in hypoxic environments. TH-302 has been evaluated as monotherapy and with cytotoxics. In relapsed/refractory SCLC, four of seven patients had stable disease (SD) or partial response (PR) with some skin toxicity and oral mucositis as dose-limiting toxicities (DLTs). There is an ongoing expansion at the maximum tolerated dose in SCLC. Phase I studies for TH-302 in combination with gemcitabine, taxotere, or pemetrexed are being conducted.

Dr. Ana Oton presented data about CS-7017, a small molecule peroxisome proliferator-activated receptor (PPAR)-γ agonist. PPAR-γ agonists are hypothesized to act by activating retinoid X receptor ligand transcription with resultant apoptosis, cell cycle arrest, and antiangiogenic changes. In vivo, CS-7017 demonstrates synergy with carboplatin and taxol. In a phase I study of 31 patients, maximum tolerated dose was not reached, with 1 PR and 12 SD. Adiponectin levels were followed as a biomarker of PPAR-γ activation, and levels increased significantly with therapy. Dr. Oton outlined several planned randomized phase II NSCLC clinical trials in the frontline (carboplatin/paclitaxel) and second-line setting (erlotinib).

Activin, a member of the transforming growth factor-B family, signals though Smad-dependent pathways and reduces bone mass through osteoblast inhibition and osteoclast stimulation. Activin A, also known as erythrocyte differentiating factor, is involved in red blood cell maturation and development. Activin overexpression has been associated with numerous malignancies.[1] Preclinically, activin stimulates cell line growth, which can be blocked with siRNA directed toward activin targets (Follistatin and INHBA). Dr. David Beer presented data related to ACE-011, a fully humanized activin antagonist. A murine version of the antibody inhibited tumor development and improved bone strength and survival in a myeloma model. Preclinical data also demonstrate improved red blood cell indices with ACE-011. Clinical studies in myeloma have been conducted, and a phase II trial for platinum-related anemia in NSCLC is planned.

Dr. Chandra Belani presented data on Volociximab, a monoclonal antibody targeting the $\alpha 5\beta 1$ integrin, with multiple effects on endothelial cell development and formation of neovasculature. In a phase Ib study, escalating doses were

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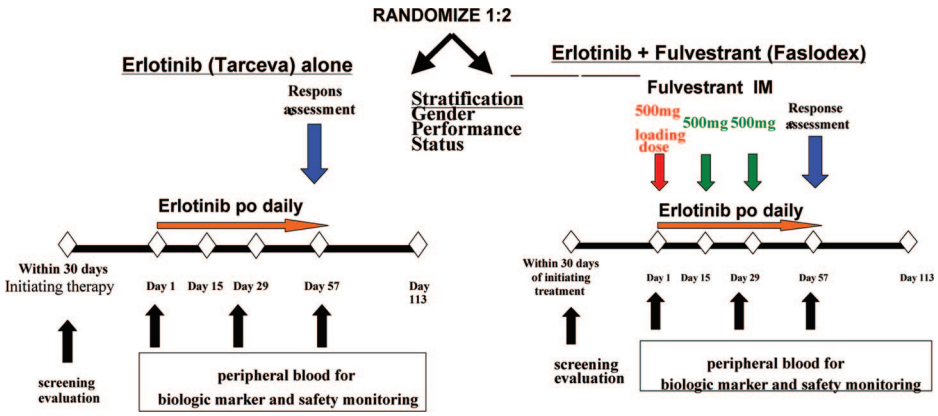

FIGURE 1. A schema of an ongoing trial of erlotinib with or without fulvestrant. Patients receive erlotinib 150 mg orally once a day with or without fulvestrant (500 mg days 1, 15, 29, and every 28 days thereafter). Patients are randomized in a 1:2 fashion and stratified for gender and performance status. Blood and tissue are being collected for correlative work.

combined with standard dose carboplatin and taxol as frontline NSCLC therapy. Three serious adverse events were attributed to the drug (arterial thrombosis, DVT), but no DLT was reached, and there were eight patients with PR (28%) and 17 with SD (57%). Further studies are planned.

Dr. Mark A Socinski presented data on three fully humanized monoclonal antibodies in NSCLC. Necitumumab has activity similar to cetuximab and is being evaluated in a phase III NSCLC trial combined with frontline pemetrexed-cisplatin (nonsquamous) or gemcitabine-cisplatin (squamous). Cixutumumab targets insulin-like growth factor receptor and is being evaluated in multiple phase II trials in NSCLC (frontline chemotherapy + bevacizumab, frontline chemotherapy plus cetuximab, and second-line erlotinib) and extensive stage SCLC (cisplatin + etoposide). IMC-3G3 targets platelet derived growth factor receptor-α with greater potency than imatinib and is being evaluated in phase II studies with cytotoxics.

Dr. Jonathan Kurie presented data on novel approaches to preventing metastatic disease. In preclinical models, the miR-200 family plays a central role in metastatic potential. Potential upstream regulators include Jagged2, and downstream targets include vascular endothelial growth factor receptor 1 and BMP4. These targets help modulate miR-200 function in coordinating interaction between tumor and stromal cells and are potential therapeutic targets.

Malignant cells must stabilize telomere length to continue replication. Up to 90% of human malignancies have detectable telomerase activity, with increased activity correlating with worse outcomes. Dr. Jerry Shay presented data on Imetelstat, a telomerase inhibitor that controls lung metastasis and leads to durable response when combined with chemotherapy in preclinical models. Imetelstat is currently being evaluated in the phase I/II setting in multiple malignancies including NSCLC, and it has demonstrated safety as a single agent or combined with cytotoxic therapy.

Dr. Roy Herbst presented data on PX-478, a novel HIF-1α inhibitor, currently the only small molecule inhibitor in this class in clinical evaluation. PX-478 inhibits HIF-1α expression in preclinical models and has substantial antitumor activity in NSCLC and SCLC xenograft models. An ongoing phase I study is nearing completion, and there were no DLTs in 40 evaluated patients.

Dr. Edward Garon presented data supporting a role of estrogen in NSCLC. In vitro and in vivo data demonstrate growth promotion effects of estrogens that are inhibited by fulvestrant. The Women's Health Initiative noted increased NSCLC mortality in women receiving exogenous estrogen therapy,[2] and observational data demonstrates that women on antiestrogen therapy for breast cancer have less risk of death from lung cancer.[3] Dr. Garon discussed an ongoing, randomized phase II trial comparing erlotinib alone or combined with fulvestrant for which extensive correlative evaluation is planned (Figure 1).

The ER pathway interacts with other growth signaling pathways (epidermal growth factor receptor, RAS-mitogen-activated protein kinase, and phosphatidylinositol 3-kinase).[4] Dr. Jill Siegfried presented data relating aromatase to lung cancer. In xenograft models, anastrozole inhibits tumor growth in ovariectomized mice, decreasing tumor number and size. Dr. Siegfried discussed a planned phase II clinical trial for postmenopausal women with advanced NSCLC who will be randomized to best supportive care or fulvestrant + anastrazole in maintenance after frontline chemotherapy.

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