Hsp90 Inhibitors

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Heat-shock proteins act as molecular chaperones to protect their substrates or client proteins from degradation in conditions of cellular stress, such as hypoxia, oxidative stress, and heat.[1] Heat-shock protein 90 (Hsp90) is expressed at increased levels in many cancers and promotes tumor growth and metastasis by stabilizing proteins necessary for tumor survival. Several well-known drivers of lung cancer tumorigenesis, such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), v-Raf murine sarcoma viral oncogene homolog B1, mesenchymal epithelial transition factor, human epidermal growth factor receptor 2 are all client proteins of Hsp90. Hsp90 inhibitors have promising activity in non–small-cell lung cancer (NSCLC) and were discussed at the Targeted Therapies Meeting in Santa Monica, 2012, in a dedicated session.

SUMMARY OF PRESENTATIONS

Dr. Sequist presented an overview of the Hsp90 pathway and its critical role in cancer cell survival in supporting oncoproteins and overcoming cellular stress. Hsp90 can buffer cancer cells from environmental stressors by promoting stability of survival pathways involved in sustaining angiogenesis, evading host immune response, promoting growth-factor independent growth, reprogramming cellular metabolism, and avoiding apoptosis. Dr. Sequist also reviewed preclinical data demonstrating the sensitivity of ALK positive NSCLC cells to Hsp90 inhibition, even in the setting of crizotinib resistance. Her discussion summarized the critical role of Hsp90 in cellular function and the rationale for its emergence as a rational target for the treatment of NSCLC.

STA-9090 (GANETESPIB)

Dr. Ramalingam described the development of ganetespib, a non-geldanamycin Hsp90 inhibitor that has demonstrated promising anticancer activity in early-phase clinical trials. This agent is associated with minimal hepatic and ocular toxicity, probably because of its unique structure when compared with older Hsp90 inhibitors. In a phase II study of ganetespib administered to previously treated stage IIIB/IV NSCLC,[2] tumor genotyping was performed to stratify patients into subgroups with EGFR mutations, K-RAS mutations, and wild type for both. Echinoderm microtubule-associated protein-like 4-ALK testing was subsequently introduced after the study was initiated. Ganetespib was tolerated well, with diarrhea being the most frequently encountered adverse event (AE). Disease stabilization was achieved in several patients with EGFR and K-RAS mutation. However, all four patients who achieved objective response, including one patient with a complete response, had ALK rearrangements. This observation is supported by the fact that in vitro data have confirmed the activity of ganetespib in ALK positive cancer cell lines.

On the basis of its promising single-agent activity, combination studies of ganetespib are currently underway. A phase I study of ganetespib in combination with docetaxel has recently been completed. The recommended phase II dose for the combination is ganetespib 150 mg/m^2 on days 1 and 15 with docetaxel 75 mg/m^2 on a 21-day cycle. The common AEs seen were grade 4 neutropenia, diarrhea, anemia, fatigue, and febrile neutropenia.[3] Promising efficacy was noted in a refractory patient population and has now led to a randomized study of docetaxel alone or in combination with ganetespib for second-line therapy of advanced NSCLC (GALAXY study–Ganetespib Assessment in Lung cAncer with docetaXel). This study is currently enrolling patients with an estimated sample size of 240 patients for the phase II part.

AUY-922

Dr. Riely discussed another novel isoxazole Hsp90 inhibitor, AUY-922. A phase I study of this agent has been completed for patients with advanced solid organs and the results were reported at the annual American Society of Clinical Oncology meeting in 2010.[4] Among the patients included in this study, nine had NSCLC; the maximum tolerated dose was 70 mg/m^2 intravenously once a week, with the most common toxicities being fatigue, diarrhea, and vision changes consisting of night blindness. A dose-related induction of Hsp70 was seen in post-treatment tissue, which indicates inhibition of Hsp90. An ongoing phase II study using AUY-922 in the third-line setting in patients with advanced NSCLC stratifies patients into molecular subgroups, based on mutations in EGFR, K-RAS, and ALK rearrangement. Another study is enrolling EGFR-mutated NSCLC patients with acquired resistance to erlotinib, to examine AUY-922 in combination with erlotinib.

DS-2248

Dr. Govindan discussed a new orally available Hsp90 inhibitor, DS-2248, developed by Daiichi Sankyo (Tokyo, Japan). This compound is being studied in a phase I trial at Wayne State University and South Texas Accelerated Research Therapeutics.[5] The trial has a two-part design, with an initial

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standard dose-escalation study in patients with advanced solid tumors, to determine a maximum tolerated dose. Once a recommended phase II dose (RP2D) is determined, the second part of the study will enroll patients with advanced NSCLC with resistance to EGFR inhibitors, erlotinib and gefitinib. The primary endpoint will be objective response rate with secondary endpoints including progression-free survival, pharmacokinetics, disease-control rate, response duration, and duration of stable disease.

IPI-504 (RETASPIMYCIN)

Dr. Heist concluded the session with a review of retaspimycin, another geldanamycin Hsp90 inhibitor. In a phase II study of IPI-504 in advanced NSCLC previously treated with EGFR inhibitors, an overall response rate of 7% was observed.[6] Interestingly, two of three patients with ALK rearrangement had partial responses, and all three patients continued therapy for at least 7 months. These results were the first to suggest that ALK positive NSCLC may represent a particularly sensitive subgroup of NSCLC to Hsp90 inhibition.

In preclinical studies, the combination of retaspimycin with rapamycin has shown promising activity in mouse tumor xenograft models of K-RAS mutated NSCLC with p53 deficiency.[7] On the basis of these findings, a phase Ib/II study is underway to examine the efficacy of IPI-504 in combination with everolimus, an mammalian target of rapamycin inhibitor, in NSCLC patients with K-RAS mutations. Once the recommended phase II dose is determined, the primary endpoint of the trial will be response rate.

At last year's annual meeting of the American Society of Clinical Oncology, Riely et al.[8] reported the results of a phase Ib trial of retaspimycin with docetaxel in previously treated NSCLC. The most commonly reported AEs were fatigue, gastrointestinal toxicities, and anemia. Six of the 23 enrolled patients achieved partial responses; the objective response rate was 43% in squamous cell carcinoma, 36% in K-RAS wild type, and 33% in smokers. This drug will be studied further in a phase II trial of advanced NSCLC patients selected for previously treated smokers who will be randomized to docetaxel with retaspimycin or docetaxel alone. The primary endpoint will be overall survival.

FUTURE DIRECTIONS

Hsp90 inhibitors have demonstrated efficacy in patients with advanced NSCLC. The results reported from the initial studies with these agents show that Hsp90 inhibition seems to benefit specific molecular subgroups of NSCLC patients. Further studies are needed to confirm these observations in larger cohorts of patients and to identify additional sensitive subsets of patients. The combination of Hsp90 inhibition with conventional chemotherapy like docetaxel is well tolerated and will be explored further for efficacy in phase II studies. Using Hsp90 inhibitors concomitantly with targeted therapies against driver mutations in NSCLC, such as with EGFR tyrosine kinase inhibitors or with crizotinib in ALK-mutated NSCLC, may also become a strategy to overcome treatment resistance in the near future.

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