tumor-bearing athymic nude mice by histological analysis. In toto, the data reveal that inhibition of the EGFR pathway with Tarceva™ provides a multipronged approach for the treatment of solid tumors by inhibiting tumor growth, survival and angiogenesis.

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EKB-569, an irreversible inhibitor of the epidermal growth factor receptor: Phase 1 trial results in patients with advanced solid tumors

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EKB-569 is a potent, selective, low molecular weight, irreversible inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. The drug inhibits the growth of tumor cells that overexpress EGFR or HER2 *in vitro* and *in vivo*. Patients (pts) with advanced solid tumor malignancies that are known to overexpress EGFR were enrolled onto a phase 1, open-label study to assess the safety, tolerability, and pharmacokinetics (PK) of EKB-569. In part 1 of the study, EKB-569 was administered orally once daily for 14 days of a 28-day treatment cycle (intermittent dosage schedule). In part 2 of the study, EKB-569 was administered orally once daily for 28 days of a 28-day treatment cycle (continuous dosage schedule). Treatment cycles were continued as long as EKB-569 was tolerated, until disease progression. For part 1 of the study, enrollment and treatment are completed; 30 pts were treated with 25 mg (7 pts), 50 mg (3 pts), 75 mg (13 pts), or 125 mg (7 pts) of EKB-569. Part 2 of the study is ongoing; 29 pts were treated with 25 mg (4 pts), 50 mg (7 pts), 75 mg (13 pts), or 100 mg (5 pts) of EKB-569. The most frequently occurring tumor types for part 1 or part 2 included colorectal, non-small-cell lung, breast, renal, and head and neck. The most frequently reported adverse events for part 1 or part 2 were diarrhea, rash, nausea, asthenia, stomatitis, vomiting, anorexia, dry skin, and dehydration. These were generally mild and reversible. Dose-limiting toxicity was grade 3 diarrhea at the 125-mg dose level in part 1 and at the 100-mg dose level in part 2, so the maximum tolerated dose was 75 mg/day EKB-569 for both parts. Two patients in part 1 and 1 patient in part 2 completed at least 6 months of treatment. Paired skin biopsy samples collected before and after EKB-569 treatment will be analyzed for phospho-EGFR levels. Pharmacokinetic assessments were performed on day 1 and day 14. For patients in part 1 of the study, concentrations in plasma on day 14 were approximately 1.5-fold higher than those on day 1. For day 14, 125 mg EKB-569, Cmax was 100 23 ng/mL (mean SD) and tmax was 6.8 1.5 h (mean SD). Distribution was extensive with mean Vss/F of 2000 to 4700 L. Mean oral clearance ranged from 73 to 155 L/h, and half-life was approximately 22 h. Additional PK and safety data will be presented. EKB-569 had an acceptable safety and PK profile, was generally well tolerated, and offers a promising targeted approach for the treatment of solid tumors.

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17AAG low target binding affinity and potent whole cell potency: finding an explanation

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The ansamycin geldanamycin (GM) and its derivative, 17AAG now in early clinical trial in cancer patients, have potent activity against several cancer cells at nanomolar concentrations. The main target of these drugs is the molecular chaperone Hsp90. Contrary to the high anti-tumor potency the affinity of these drugs for the chaperone was determined to be around 1uM. We propose that this discordance can partly be explained by the chemical characteristics of the ansamycins. GM and 17AAG are hydrophobic in nature and therefore, highly water insoluble. Upon addition to media they accumulate into cells, resulting in higher intracellular concentrations than expected. We conclude that the real potency of ansamycins correlates with their Hsp90 binding affinity and is in the low micromolar concentration range. We suggest that in the clinic micromolar amounts of 17AAG at the site of the tumor will be necessary to see anti-tumor effects in patients comparable to ones achieved in tissue culture settings.

Regulatory affairs

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The cancer therapy evaluation program initiatives for enhancing industry collaborations

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The Cancer Therapy Evaluation Program (CTEP) of the Division of Cancer Treatment and Diagnosis, National Cancer Institute has recently instituted and/or revised a number of initiatives designed to enhance CTEP's interactions with Industry Collaborators. These initiatives are in response to the concerns voiced by Collaborators considering collaborations with CTEP, including intellectual property issues, access to data, combination studies, indemnification, and others. In response to concerns regarding intellectual property issues, CTEP has developed a document entitled Intellectual Property Option to Collaborators (the Option) which offers rights of first negotiation to a license to any invention by an extramural investigator to the Collaborators whose agent was used for clinical trials which resulted in an invention. This option is now in place for all Phase 1 and 2 contracts, as well as all Cancer Center grants, Cooperative Group and Cancer Trials Support Unit agreements. A modification of the'Option' for studies involving the combination of proprietary agents is currently under way. Further, this has been extended to cover preclinical studies under CTEP-sponsored agreements. Revisions have been made to electronic data submission contracts to permit Collaborators frequent access to data from CTEP-sponsored Phase 1 and 2 studies to address industry needs for rapid data access. Expedited adverse events are now reported electronically via a web-based system (AdEERS). AdEERS is currently being modified to allow Collaborators simultaneous access to safety reports. More detailed information on these and other initiatives will be presented.

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The Adverse Event Expedited Reporting System (AdEERS) of the cancer therapy evaluation program

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The Cancer Therapy Evaluation Program (CTEP) of the Division of Cancer Treatment and Diagnosis (DCTD), NCI has developed and implemented a web-based system, the Adverse Event Expedited Reporting System (AdEERS), for the electronic reporting of expedited adverse events for all clinical trials using a CTEP-sponsored investigational agent. AdEERS is designed to support the classification, retrieval, and evaluation of adverse event information using the standard language of MedDRA (Medical Dictionary for Regulatory Activities terminology). In addition, AdEERS is integrated into the existing CTEP Enterprise applications including the Common Toxicity Criteria (CTC, v2.0) and the Clinical Data Update System (CDUS). AdEERS provides an assessment section to help users determine whether the event requires expedited reporting based on the expectedness of the event and the NCI Adverse Event Reporting Guidelines. Two pathways of submission of expedited reports are supported by AdEERS - central processing as used by the Cooperative Groups/Consortia and non-central processing used by single institutions. The security of AdEERS is ensured using SSL 128 bit encryption. A random ticket number is automatically generated for each report. Users can access a particular report by using a combination of the ticket number, the patient identifier, and the CTEP protocol number. The system can be accessed using industry standard browsers on systems running Windows, Netscape v4.x and above or Internet Explorer v5.x and above. AdEERS was implemented on January 1, 2001 for all CTEP-sponsored investigational agent studies. In CY 2001, CTEP received approximately 3900 reports. AdEERS is being piloted with the FDA and has been demonstrated to other potential users at NIH. The development of xml tags is in process and should facilitate the transfer of AdEERS data to the FDA, pharmaceutical collaborators, and others.