three cell lines – 22RV1 cells (SER: 1.2), DU145 cells (SER: 1.3) and GM5757 (SER: 2.0). Combined treatment with Nutlin-3 and Radiation (5 μM + 6 Gy) increased apoptotic fraction of 22RV1 from 1% to 21% as compared to radiation (12%) or Nutlin-3 alone (7%), apoptosis was not altered in DU145 and GM5757. In contrast, preliminary data suggests that the mechanisms of sensitization may include increased mitotic catastrophe. Current experiments are determining whether radiosensitzation is also observed under hypoxic conditions prior to tumour xenograft studies.
**Conclusion:** Nutlin-3 is a potent radiosensitizer of prostate cancer cells regardless of p53 status. This suggests that Nutlin-3 can act via p53- and p21WAF-independent mechanisms. The observed radiosensitization of a normal fibroblast strain suggests that confirmatory studies in vivo be conducted with both tumour and normal tissue endpoints.

# Regulatory affairs

**540** POSTER

**Novel investigational agent clinical trials: cancer therapy evaluation program initiatives to enhance combination studies**

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The Cancer Therapy Evaluation Program (CTEP) of the Division of Cancer Treatment and Diagnosis, National Cancer Institute has made the evaluation of rational combinations of molecularly targeted agents a high priority. Because most such agents are being developed by the pharmaceutical/biotechnology industry, this often requires the agreement and cooperation of 2 or more pharmaceutical companies. Because CTEP sponsors over 125 active Investigational New Drug applications (INDs), it is in an unique position to facilitate the combination of investigational agents for multiple therapeutic target types. In order to facilitate preclinical and clinical studies involving the novel combinations of promising investigational anticancer agents originating from more than one pharmaceutical collaborator, CTEP has created standard intellectual property agreements. All collaborative clinical agreements between CTEP and pharmaceutical collaborators include provisions to facilitate mutually agreeable combination studies, both preclinical and clinical, sponsored by the NCI without the need to negotiate additional agreements between the collaborators, CTEP, or the investigative site. One of the key provisions that encourages such studies is a modification of the basic Intellectual Property Option to Collaborator (the Option) which provides all collaborators contributing an agent for a combination study with a non-exclusive royalty free license to any invention that might arise using the combination. Furthermore, the Option also applies to preclinical studies designed to provide data in support of a clinical trial. In addition, CTEP includes provisions for data sharing with all collaborators in all collaborative agreements. Thus, the need for collaborators to negotiate cumbersome and time-consuming intellectual property or data sharing agreements with each other or the site conducting the study prior to approving such studies has been eliminated. Such arrangements have led to the initiation of over 100 investigational agent combination protocols. Current data on the volume and frequency of these studies is illustrated, as well as the mechanisms and terms by which these agreements are modeled and implemented.

# Signal transduction modulators

**541** POSTER

**Pulmonary changes in a randomized phase II study of the mTOR inhibitor RAD001C (Everolimus): NCIC CTG IND.163**

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**Background:** mTOR inhibitors may be associated with pulmonary toxicity, particularly pneumonitis (PN). PN is poorly described in the literature. While many patients (pts) are asymptomatic with nonspecific findings noted incidentally on thoracic imaging, others may present with symptoms that include dry cough and/or dyspnea. Severe cases can result in hypoxia necessitating drug discontinuation, corticosteroid therapy and hospitalization. In our ongoing randomized study of an mTOR inhibitor, 3 cases of possible PN were noted, prompting a safety review.
**Methods:** A review of medical records and radiological reports was conducted on 34 pts enrolled on NCIC CTG IND.163, a single-agent phase II study evaluating two schedules of administration (Arm A: 10 mg p.o. daily; Arm B: 70 mg p.o. weekly) of RAD001C for the treatment of metastatic breast cancer.
**Results:** From January to November 2005, 34 women with metastatic breast cancer were treated with RAD001C (Arm A: n = 18; Arm B: n = 16) in part 1 of the study. Fifteen pts (44%) developed clinical and/or radiological changes suggestive of possible PN (Arm A: 12, 67%; Arm B: 3, 19%). Of these 15 pts, 11 (73%) received at least one previous anthracycline-containing chemotherapy regimen and 12 (80%) received radiation to the ipsilateral breast or chest wall; 4 pts (27%) were asymptomatic, whereas 11 (73%) had either dry cough and/or dyspnea, usually grade 1 or 2 ($G_1$ or $G_2$). Radiological changes consisted of patchy airspace consolidation, ground-glass opacities or diffuse interstitial disease. Of the 15 pts with possible PN, 4 discontinued study drug due to PN ($G_2$=3, $G_3$=1), 1 due to $G_3$ left ventricular dysfunction, 7 due to disease progression (worst PN: $G_1$=4, $G_2$=3) while 3 pts continue on treatment (all $G_2$ PN) without worsening PN. Most pts with $G_1$ and $G_2$ PN were managed expectantly whereas 3 women ($G_2$=2, $G_3$=1) were treated with corticosteroids. Two pts required hospitalization. Symptoms and radiological changes cleared after drug discontinuation. No pts have been rechallenged.
**Conclusions:** In this trial, RAD001C appeared to be associated with schedule dependent pulmonary changes consistent, in some cases, with drug-induced PN. The clinical severity of presentation was variable while the findings were, in general, reversible. Protocol modifications for part 2 of the study have been implemented. The potential for pulmonary toxicity should be considered when designing future trials with this class of agent.

**542** POSTER

**A randomized phase II study of two different schedules of RAD001C in patients with recurrent/metastatic breast cancer**

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**Background:** RAD001C is a macrolide antibiotic that exerts antiproliferative effects by mTOR (mammalian target of rapamycin) inhibition, and antiangiogenic effects by inhibition of endothelial cell proliferation. mTOR is critical in the transduction of proliferative signals mediated via the PI3K/Akt pathway. This signal transduction pathway is relevant to HER2 and ER signaling, and in PTEN mutant tumours, so mTOR may be a central and relevant factor in breast cancer.
**Methods:** Multi-centre randomized phase II study assessing two oral schedules of RAD001C: Arm A (A): 10 mg daily, or Arm B (B): 70 mg weekly, assessed clinically each 4 weeks, imaged each 8 weeks. Eligibility: Patients (pts) with measurable metastatic breast cancer (MBC) who may have received adjuvant chemotherapy (chemo), with up to one prior chemo for advanced/recurrent disease. Stratification factors: 0 or 1 prior chemo for MBC; presence/absence of visceral metastases. Primary endpoint: clinical/radiologic response and early progression (<8 wks). Two-stage accrual design with 15 evaluable pts in each arm in first phase. If $\geqslant$1 response and <10 early progressors, continue arm and enter 15 more pts. If 1 arm stopped after first phase, continue non-randomized accrual to remaining arm.
**Results:** First phase of accrual complete with A: 18 and B: 16. Number of prior chemo regimens (0/1/2): A: 3/11/4; B: 3/7/6. Visceral/bone/nodal metastases: A: 11/9/14, B: 17/6/9. Median number of cycles: A: 3 (1–9), B: 2 (2–9). 3 partial responses and 7 early progressors were seen in A and 0 responses and 11 early progressors in B. Median SD duration for A: 5.7 months (range 3–7.1) and B: 5.1 months (range 3.4–7.3). Discontinued therapy: A: 15 off, 9 for PD, 4 for AE (grade 3 pneumonitis (PN), grade 2 PN $\times$ 2 pts, grade 3 left ventricular systolic dysfunction), 2 symptomatic progression. B: 16 off, 13 for PD, 2 for AE (grade 2 PN, grade 4 fatigue), 1 symptomatic progression. Toxicities (nausea, stomatitis, diarrhea, rash, cough, neutropenia) were generally mild, similar between arms, and as expected, except for higher than expected incidence of clinical and/or radiologic PN (A: 67% and B: 19%).
**Conclusions:** Early findings indicate RAD001C has activity in MBC. Criteria for expanding Arm A were met. PN was more frequent in arm A, the daily schedule. Accrual to Arm A will continue with close monitoring and consideration of early intervention for those patients who develop radiologic changes of PN.