Conclusion: Concurrent STK11 loss and c-MYC amplification in NSCLC is uncommon, but had no impact on survival in a limited patient set. This study underscores the importance of large-scale, clinically annotated genomic data sharing initiatives in systematically exploring the clinical relevance of rare genomic alterations.

B09
The CANOPY Program: Three Phase 3 Studies Evaluating Canakinumab in Patients with Non-Small Cell Lung Cancer (NSCLC)

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Background: Canakinumab (CANA) is a selective IL-1 receptor antagonist that aims to target tumor-promoting inflammation to reduce immune suppression. In the CATSOS study, CANA treatment was associated with reduced lung cancer incidence and mortality in patients (pts) with stage post-myocardial infarction who had elevated high-sensitivity C-reactive protein levels, thus providing a rationale to investigate its possible therapeutic role in lung cancer. Methods: CANOPY-A, CANOPY-1, and CANOPY-2 are phase III, multicenter, randomized, double-blind, placebo-controlled studies. In CANOPY-A, pts (~1,500) with stages IIA–IIIA and IIIB (T 4 N2), any histology, completely resected (RO) NSCLC, who received cisplatin-based chemotherapy (CTx), will be enrolled and randomized 1:1 to receive either CANA (200 mg Q3W SC) or placebo + docetaxel. As of Oct 23, there are 85 study locations per clinicaltrials.gov. In part 1 (both studies), the primary endpoint is the incidence of dose limiting toxicities in the first 42 days of treatment. In part 2, the primary endpoints are progression-free survival (PFS) and OS in CANOPY-1, and OS in CANOPY-2. Common secondary endpoints (both studies) include overall response rate, disease control rate, time to response, duration of response, PFS (CANOPY-2), pharmacokinetics, safety, patient-reported outcomes, and immunogenicity. All three studies (CANA-A, CANOPY-1, and CANOPY-2) are currently recruiting.

B10
Prevalence of EGFR Mutation Among Vietnamese Non-Small Cell Lung Cancer: A Preliminary Study

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Aims: To investigate the distribution of epidermal growth factor receptor (EGFR) mutations, and explore any relationships with characteristics of non-small cell lung cancer (NSCLC) patients. Materials and Methods: EGFR mutations were assessed by Scorpios and ARMS technologies (therascreen® EGFR RQ PCR Kit - Qiagen) in randomized sample block of 200 NSCLC patients from Vietnam National Cancer Hospital. Relationships between EGFR mutation and patient characteristics were analyzed by R statistical software. Results: The EGFR mutation rate was 41% (83/200); 19-del and L858R mutations occurred predominantly, accounting for 55.4% and 27.2%, respectively, in mutated cases. Moreover, 3.5% patients were found to carry double mutations. EGFR mutations occurred more frequently in women (75%) than in men (27.1%) (P < 0.001). Mean ages of patient with mutation and without mutation were 56.51 (±8.86) and 58.83 years (±9.05), respectively (p = 0.073). Gender distribution was significantly different between the 2 groups of mutation and no mutation (p < 0.001). In EGFR mutation group, 98.8% of them possessed the Vietnamese health insurance and 9.6% of them which their first diagnosis had no relation with lung carcinoma. Conclusions: The EGFR mutation rate was 41% in NSCLCs in Vietnam, so that about 40% of patients might benefit from targeted therapies. Further studies are required to have a comprehensive understanding about the other clinical characteristics and EGFR mutation in Vietnamese patients.

B11
Accurate Detection of METex14 Mutations in Non-Small Cell Lung Cancer (NSCLC) with Comprehensive Genomic Sequencing: Results from the GEOMETRY Mono-1 Study

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Background: MET exon 14 skipping mutations (METex14) occur in 3–4% of patients (pts) with NSCLC. Accurate detection of the genomic variants that result in METex14 in MET-driven tumors could facilitate timely intervention with selective MET inhibitors (METIs) and improve
clinical outcomes. Different detection assays for METex14 using various platforms have yielded mixed results across studies. It is imperative to utilize reliable and validated molecular assays to identify pts to be treated with METL. RNA-based detection of METex14 is considered the gold standard, since this assay measures the direct result of deletion of exon 14 event regardless of underlying genomic events. DNA-based next-generation sequencing (NGS) must detect genomic alterations within MET exon 14 and adjacent intronic regions that alter a splicing site or delete the whole MET exon 14. Methods: The GEOMETRY mono-1 study evaluated the efficacy and safety of capmatinib in pts with EGFR-wt, ALK-neg, NSCLC harboring METex14. This retrospective analysis compared DNA-based NGS with RNA-based RT-PCR in detecting METex14 in the GEOMETRY mono-1 study. Eligible METex14-mutated pts confirmed by RT-PCR qualitative assay using RNA extracted from baseline formalin-fixed, paraffin-dipped (FFPE) tissue samples were assigned to cohorts 4 (C4; previously treated) or 5b (C5b; treatment-naïve), independent of MET amplification status. Retrospectively, METex14 positive and prescreen failed negative base line FFPE tissue samples were tested using a hybrid capture DNA-based NGS assay (FoundationOne®). The METex14 positive pts by DNA NGS were defined as having MET alterations that are predicted to lead to MET exon 14 skipping. Results: Of the 97 enrolled pts from the METex14-mutated cohorts C4 (n=69) and C5b (n=28) of the GEOMETRY mono-1 study, 73 pts had baseline tumor biopsy samples (C4, n=53; C5b, n=20) that met the requirements for the FoundationOne® NGS assay (minimum requirements: tumor volume ≥0.1 mm³, DNA yield ≥22 ng, percent tumor nuclei ≥10). The FoundationOne® NGS assay identified METex14 in 72 of 73 positive pts, with a concordance of 99% to the qualitative RT-PCR test used previously for testing. The variants detected included 41 unique canonical alterations that are predicted to lead to METex14. 1 pt with only a noncanonical METex14 rearrangement was not included in the concordance analysis and reported stable disease. None of the RT-PCR negative patients were reported as positive by NGS. Conclusions: Detection of MET exon 14 skipping events can be achieved by sequencing DNA or RT-PCR. A very high concordance was observed between DNA-based hybrid-capture NGS and RNA-based RT-PCR in the detection of METex14 in FFPE tumor tissue from advanced NSCLC pts. NGS enables parallel detection of actionable alterations without sequential testing by single gene. Furthermore, this technique provides a comprehensive genomic profile to inform treatment plan and any potential mechanisms of resistance.

B13 Selectively Targeting Lung Cancer with a Novel Small Molecule that Induces Lethality Through Dual Inhibition of Disulfide Reductases

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Lung cancer (LC) is the leading cause of cancer-related deaths worldwide, mainly due to the lack of effective therapies. Through a screen of 189,290 small molecules, the compound LC Screen 3 (LCS3) that inhibits the growth of LC cells but not normal cells was identified. LCS3 is structurally unique and its mechanism of action is unknown. Twenty-six lung adenocarcinoma cell lines were screened, and all but two were found to be sensitive to LCS3 (IC50<5μM). Transcriptome and proteome profiling by microarray and SILAC, respectively, suggest that LCS3 strongly induces redox imbalance. The top four predicted upstream transcriptional regulators of LCS3-induced RNA expression changes all have key functions in the response to oxidative stress (NRF2, MAPK, CEBPB, and BACH1). We confirmed LCS3 induces NRF2 activation through Western blot and flow cytometry analyses using a stably expressed antioxidant response element GFP reporter. In addition, flow cytometry with oxidative stress sensor H2DCFDA detected reactive oxygen species (ROS) induction by LCS3 only in sensitive cell lines. Notably, the most resistant LC cell line, NCI-H1648, has biallelic functional loss of KEAP1, which negatively regulates NRF2-mediated cytoprotective gene expression. We confirmed that NCI-H1648 has low basal ROS and high basal expression of genes that support redox balance. KEAP1 silencing and antioxidants including N-acetylcysteine partially rescued LCS3-induced cytotoxicity, which further implicates oxidative stress in the mechanism of LCS3-induced cell death. To elucidate the molecular targets of LCS3, we applied thermal proteome profiling (TPP), which identifies thermally stabilized protein binders with proteome-wide coverage, and identified 47 proteins that are putative binders of LCS3. Of the 47 TPP hits, 8 are enzymes that function in redox homeostasis. Through in vitro enzymatic assays of the top TPP hits, we discovered that LCS3 inhibits glutathione disulfide reductase (GSR) and thioredoxin reductase 1 (TXNRRD1) through reversible, uncompetitive inhibition at low micromolar IC50s. In silico molecular docking suggests LCS3 interacts with the GSR homodimer interface, and our structure-activity relationship studies have identified the putative functional moiety on LCS3 necessary for both enzymatic inhibition and cellular toxicity. We found that Luperox, a direct-acting hydroperoxide source of ROS, sensitizes nonresponsive cells to LCS3, thus implicating ROS as a requirement for LCS3-mediated toxicity. We are currently investigating why nonresponsive cells are less dependent on the glutathione and thioredoxin pathways and how oncogenic transformation, and the inherent oxidative stress that coincides, confers sensitivity to dual disulfide reductase inhibition. Through this work, we

B12 FOXA2 Promotes the Growth of KRAS-Mutant Lung Tumors But Suppresses the Growth of EGFR-Mutant Lung Tumors in Vivo

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Background: Using GEMM (Genetically Engineered Mouse Models), we showed that a lung-lineage transcription factor NKX2-1 promotes the growth of EGFR-mutant lung tumors but suppresses the growth of KRAS-mutant lung tumors in vivo (Maeda et al, JCI 2012), suggesting that such transcription factors expressed in the lung act as a context-dependent tumor promoter or suppressor. Here, we report the roles of a pioneer transcription factor FOXA2 expressed in lung epithelium in KRAS-mutant or EGFR-mutant lung tumors in vivo. Methods: Using doxycycline-regulatable GEMM expressing mutant KRAS or mutant EGFR along with FOXA2 in lung epithelium (CCSP-rtTA; otet-KrasG12D; otet-Foxa2 or CCSP-rtTA; otet-EGFR.L858R; otet-Foxa2), we assessed whether FOXA2 influenced the growth of KRAS-mutant or EGFR mutant lung tumors in vivo. The number and size of lung tumors were analyzed by microCT. The histology of the lung tumors was further analyzed by H&E and immunohistochemistry. Results: FOXA2 induced an increase in volume but not the number of KRAS-mutant lung tumors associated with lung adenocarcinoma while FOXA2 reduced the volume and number of EGFR-mutant lung tumors in vivo. Phosphohistone H3 was increased in KRAS-mutant lung tumors but decreased in EGFR-mutant lung tumors by FOXA2. Caspase-3 was not affected. These results indicate that FOXA2 differentially influences the initiation and progression of lung tumor growth depending on the type of driver oncogenes (mutant KRAS vs. mutant EGFR) in part through proliferation but not apoptosis. Conclusion: Transcription factors NKX2-1 and FOXA2 function as yin and yang to affect the growth of KRAS-mutant or EGFR-mutant lung tumors.

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