37MO Concurrent mutations in STK11 and KEAP1 promote ferroptosis protection and SCD1 dependence in lung cancer

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Background: STK11 and KEAP1 loss are strongly co-associated ($p<0.001$) in lung adenocarcinoma (LUAD). Our team has found that in a 468-gene panel, co-occurrence of these two mutations is the strongest driver of poor outcome in LUADs, conferring resistance to both standard chemotherapy and immunotherapy, resulting in an average overall survival of less than 8 months from diagnosis. Little is known about the cooperativity and an in-depth understanding of the biological and functional consequences of STK11 and KEAP1 co-mutation is an urgent clinical need that is essential to identify effective therapeutic targets.

Methods: We sequentially profiled 1,235 patients with metastatic LUAD by next generation sequencing (MSK-IMPACT). We used CRISPR/Cas9 to create stable knockouts of STK11, KEAP1, or both genes, in three LUAD lines. We performed cell proliferation, bulk RNAsequencing. Furthermore, we performed CRISPR/Cas9 screens in isogenic in vitro models using a curated "druggable genome" sgRNA library that targets 1,463 genes.

Results: STK11/KEAP1 co-mutation predicts short overall survival in patients with LUAD. STK11/KEAP1 co-mutation promotes tumor cell proliferation and migration in vitro and significantly enhanced tumor growth in vivo. Bulk RNA sequencing demonstrated that STK11/KEAP1 co-mutant cells have higher expression of genes involved in ferroptosis protection and are resistant to ferroptosis inducing agents. CRISPR/Cas9 screen identified ferroptosis regulator SCD as an essential gene required for proliferation and survival of STK11/KEAP1 co-mutant cells. Genetic and pharmacological inhibition of SCD1 prevented the growth of STK11/KEAP1 co-mutant cells and sensitized these cells to ferroptosis induction. Finally, in vivo inhibition of SCD1 significantly delayed tumor growth in STK11/KEAP1 co-mutant LUAD.

Conclusions: This study describes, for the first time, ferroptosis evasion as a survival mechanism for STK11/KEAP1 mutant tumors. We identify SCD as an essential gene in STK11/KEAP1 co-mutant LUAD. SCD1 inhibition, either alone or in conjunction with agents targeting ferroptosis, represents a promising strategy to improve outcomes in this cohort of patients with limited therapeutic options and poor prognosis.

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38MO IND.236: A Canadian Cancer Trial Group (CCTG) phase Ib trial of combined CFI-402257 and weekly paclitaxel (Px) in patients with HER2-negative (HER2-) advanced breast cancer (BC)

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Background: CFI-402257 (CFI) is a selective oral inhibitor of TTK protein kinase, a critical regulator of the mitotic spindle assembly checkpoint, is overexpressed in BC and enhances activity of Px in BC xenografts.

Methods: Define recommended phase II dose (RP2D) of CFI in combination with weekly Px using 3+3 escalation. Patients with HER2- advanced BC with adequate organ function, PS=0-1, previously treated with 1 or more non-taxane chemotherapy, were eligible. CFI was given on a 2-day on, 5-day off schedule with Px 80mg/m^2 on day 1, 8, 15 every 28 days. Starting dose, based on the CFI phase I study, was 84mg PO. Five dose levels (DL) were planned: 84, 112, 168, 210 and 252mg.

Results: 29 patients received a total of 169 cycles. Median age was 58 years; 90% ER+/HER2-; 45% PS=1; 21% 3 or more prior chemotherapy regimens (76% received CDK4/6 inhibitors). Grade (G) 3 or more ANC was reported in 66%, G4 in 39%, and 2 patients had infection (febrile neutropenia and skin). Five patients met criteria for dose limiting toxicity (DL3=2; DL4=2; DL5=1): all were G4 ANC. ANC appeared dose dependent and G4 ANC was only reported in DL3, 4 and 5. Increased age was also associated with higher likelihood of G4 ANC (median age of patients with G4 ANC 68 years vs. 51 years; p=0.0025). Adverse events related to CFI and or Px G2 or more included: alopecia (3%), fatigue (10%) and nausea (3%). Partial response was reported for 3 patients.

Conclusions: CFI plus Px has a manageable toxicity profile, with anticancer activity in this heavily pretreated population. Expansion at DL3 (168mg) is ongoing; updated safety/efficacy data will be presented at the meeting.

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Legal entity responsible for the study: Queen's University.

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39P Effect of dose level of the selective FGFR2 inhibitor alofanib on toxicity, pharmacokinetics and preliminary efficacy: A phase Ib study in patients with advanced gastric cancer (RPT835GC1B)

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Background: FGFR2 molecular changes was observed in gastric cancer at a frequency of 4-15% and associated with shorter progression-free survival (PFS) and overall survival (OS). Alofanib (RPT835) is a novel selective inhibitor that binds allosterically to the extracellular domain of FGFR2.

Methods: The aim of this phase Ib study was to determine dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, preliminary efficacy and pharmacokinetics (PK) of alofanib administered intravenously daily for 5 days weekly. Patients with advanced or metastatic gastric adenocarcinoma resistant to standard therapy were enrolled in 5 dose levels: 50, 100, 165, 250, and 350 mg/m2, using a 3+3 design.

Results: To date, 13 patients have been enrolled in the trial. The MTD was not reached. All patients have not experienced any DLT within the 28-day DLT-assessment window. Intravenous alofanib was safe. There were no correlations between dose level and toxicity. Three grade 3 adverse events (ALT/AST increased at 50 mg/m2, diarrhea at 165 mg/m2, and hyponatremia at 350 mg/m2) were reported. One patient discontinued treatment due to drug related grade 3 uncontrolled diarrhea. Grade 1-2 adverse events included fatigue, diarrhea, nausea, anemia, thrombocytopenia, increased alkaline phosphatase, and reactions immediately after intravenous injections (facial flushing, dizziness, weakness, sweating, and sinus tachycardia). Grade 1 hyperphosphatemia was founded in 25% of cases. Of the 12 assessed patients, 1 (8%) partial response at 50 mg/m2 and 8 (67%) stable diseases at 50-250 mg/m2 were recorded. After a median follow-up of 4.5 months, the median PFS and OS was not reached. PK parameters have increased with dose. PK values (Cmax, AUC, and t1/2) did not correlate with response, PFS and OS (all $P>0.1$).

Conclusions: Administration of alofanib by intravenous route as single agent was safe and demonstrated promising antitumor activity in heavily pretreated patients with metastatic gastric cancer. The MTD has not been reached up to 350 mg/m2. PK profiles did not correlate with toxicity and efficacy of alofanib. The study is ongoing.

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Legal entity responsible for the study: Ministry of Health, Russian Federation.

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40P Phase I study of the safety, pharmacokinetics and pharmacodynamics of escalating doses followed by dose expansion of selinexor in Asian patients with advanced solid tumour malignancies

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Background: This study was conducted to evaluate the tolerability of selinexor and to establish the recommended phase II dose in an Asian population.

Methods: We investigated 4 dosing schedules. Schedule 1: twice a week dosing at 40mg/m2 in a 28-day cycle. Schedule 2: once weekly at 50mg/m2 in a 28-day cycle. Schedule 3: twice a week dosing at 40mg/m2, 2 out of 3 weeks in a 21-day cycle. Schedule 4: 3 times a week dosing at 20mg/m2 in a 28-day cycle. Adverse events were graded with the NCI Common Terminology Criteria for Adverse Events v 4.03. Pharmacodynamic assessments: nuclear-cytoplasmic localisation of p27, XPO1 cargo proteins including ki67, apoptag, cleaved caspase 3, and c-myc pre and post selinexor. Pharmacokinetic assessments were conducted in 19 individuals at doses between 40-60mg/m2.

Results: The safest dosing was 40mg/m2 (equivalent 60mg) with no DLTs. The schedule with a 1-week drug holiday was the most tolerable for our patients. G3 adverse events included fatigue (8%), hyponatremia (23%), vomiting (5%), thrombocytopenia (5%), anemia (2%). Selinexor had a rapid oral absorption with median T_{max} of 2 h with no PK accumulation after multiple doses of tested regimens. Complete responses were noted in 2 lymphoma patients. Partial responses were noted in 3 DLBCL patients, 1 Hodgkins lymphoma and thymic carcinoma. Stable disease was seen in 12 colorectal cancer patients, 3 pancreatic cancer patients, 2 thymic carcinoma patients, 1 each for ovarian cancer, hepatocellular carcinoma, cholangiocarcinoma, lung cancer, breast cancer, tongue cancer and grey zone lymphoma. An exploratory analysis on 36 colorectal cancer cases with known RAS pathway mutational status showed a median progression free survival of 86 vs 50 days, p=0.09, log-rank in RAS mutant compared to wildtype patients.

Conclusions: Selinexor is tolerated by Asian patients at 60mg twice a week. A 1-week drug holiday was needed as our patients could not tolerate the continuous dosing regimens because of persistent G3 fatigue, anorexia and hyponatremia. Exploratory analyses of colorectal cancer patients alluded to a clinical benefit that selinexor may have significant activity in RAS pathway activated tumors.

Legal entity responsible for the study: The authors.

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41P The functional GRHL3-FLG axis predicts targeted therapy response in head and neck cancer

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Background: Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease harbouring the most frequent hotspot mutations in the differentiation genes. Disruption of epithelial differentiation acts as a primary driver of HNSCC development and correlates with a poor patient's prognosis. To date, in addition to the non-selective conventional HNSCC treatments, such as chemotherapies and surgeries, the only FDA-approved targeted therapy Cetuximab, an epidermal growth factor receptor inhibitor, has a low response rate with considerable toxicity. Therefore, determining whether functional differentiation can serve as a molecular vulnerability and/or a predictor of targeted therapy in HNSCC is an area of valuable clinical need.

Methods: A multi-omic approach integrating whole-genome and whole-transcriptome sequencing with drug sensitivity screening was employed in tumours from a spontaneous HNSCC murine model, HNSCC patient's tumours, and established human cell lines to reveal potential predictive biomarkers for targeted therapies. CRISPR-Cas9-mediated gene knockout and activation validated candidate predictors in HNSCC cell lines treated with inhibitors of the PI3K/mTOR, c-MYC and STAT3 pathways, the key signalling in HNSCC oncogenesis.

Results: We identified a novel Grainyhead-like 3 - Filaggrin (GRHL3-FLG) differentiation axis as a predictive biomarker to targeted therapy response in HNSCC. A subset of HNSCC with functional GRHL3-dependent differentiation was the most sensitive to inhibitors of PI3K/mTOR, c-MYC and STAT3 signaling. Furthermore, we identified the GRHL3 transcriptional target gene FLG as a novel tumour differentiation gene and, more importantly, stratified HNSCC subsets as treatment-resistant based on their FLG mutational profile. Moreover, the loss of FLG in sensitive HNSCC cells resulted in a dramatic resistance to targeted therapies while the $GRHL3^{hi}$-FLG^{wt} signature predicted a favourable patient's prognosis.

Conclusions: Functional differentiation ($GRHL3^{hi}$-FLG^{wt}) provides the first example of differentiation-dependent therapy response and establishes a rationale for clinical investigation of differentiation-paired targeted therapy that may improve outcomes in HNSCC and other heterogeneous cancers.

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42P Using patient-reported outcomes (PROs) in phase I/II dose-finding oncology trials (DPOT): A global survey

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Background: Patient-reported adverse events may be a useful adjunct for assessing a drug's tolerability in DPOT. A review of DPOT registered on clinicaltrials.gov showed increasing use of PROs over time, but overall use remained limited. Little is known about the reasons for limited PRO use. We conducted a global online survey of key stakeholders to understand attitudes towards PROs in DPOT.

Methods: A 35-question survey of clinicians, trial managers, statisticians, funders and regulators involved in DPOT in hospitals, academia or industry distributed via professional bodies. Questions focussed on prior experience of designing, conducting and reporting DPOT with PROs, attitudes towards benefits and barriers to PRO use and their potential role in defining tolerable doses. Adaptive questioning was used. No identifiable data was collected.

Results: 112 responses from 15 September to 30 November 2020; 103 trialists [48 clinicians (42.9%), 38 statisticians (34.0%), 17 trial managers (15.2%)], 7 regulators (6.3%) and 2 funders (1.8%). Most had worked in DPOT for 6-10 years (35, 31.3%). Most worked in the United Kingdom (65, 58.0%) or United States (22, 19.6%). Most trialists had no prior experience designing (73, 70.9%), conducting (52, 50.5%) or reporting (88, 85.4%) PROs in DPOT. Respondents strongly agreed/ agreed that PROs could identify new toxicities (75, 67.0%), provide data regarding frequency (86, 76.8%) and duration (81, 72.3%) of toxicities, especially in agents with moderate, chronic or delayed toxicities (77, 68.8%). Respondents agreed that PROs should be reviewed when making dose-escalation decisions (61, 54.5%), when determining the maximum tolerated dose (63, 56.3%) and recommended phase II dose (76, 67.9%). Top 5 concerns were: lack of guidance regarding PRO selection (73/103, 70.9%), missing PRO data (79/112, 70.5%), overburdening staff (68/103, 66.0%) or patients (57/103, 55.3%), and analysis and publication (58/112, 51.8%).

Conclusions: Key stakeholders reported minimal experience collecting and analysing PROs in DPOT. However, there was broad support for using PROs to inform selection of tolerable doses. Guidelines are needed to standardise selection, analysis and reporting, and increase efficiency of PRO collection in DPOT.

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