

9th European Scientific Oncology Conference (ESOC-9)

KURA ONCOLOGY

Targeting the RAS-ERK Pathway

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FORWARD-LOOKING STATEMENTS

This presentation contains forward-looking statements. Such statements include, but are not limited to, statements regarding our research, pre-clinical and clinical development activities, plans and projected timelines for tipifarnib, and our other programs, plans regarding regulatory filings, our expectations regarding the relative benefits of our product candidates versus competitive therapies, and our expectations regarding the therapeutic and commercial potential of our product candidates. The words "believe," "may," "will," "estimate," "plan", "continue," "anticipate," "intend," "expect," "potential" and similar expressions (including the negative thereof), are intended to identify forward-looking statements. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Risks that contribute to the uncertain nature of the forward-looking statements include: our future preclinical studies and clinical trials may not be successful; the U.S. Food and Drug Administration (FDA) may not agree with our interpretation of the data from clinical trials of our product candidates; we may decide, or the FDA may require us, to conduct additional clinical trials or to modify our ongoing clinical trials; we may experience delays in the commencement, enrollment, completion or analysis of clinical testing for our product candidates, or significant issues regarding the adequacy of our clinical trial designs or the execution of our clinical trials may arise, which could result in increased costs and delays, or limit our ability to obtain regulatory approval; our product candidates may not receive regulatory approval or be successfully commercialized; unexpected adverse side effects or inadequate therapeutic efficacy of our product candidates could delay or prevent regulatory approval or commercialization; we may not be able to obtain additional financing. New risk factors and uncertainties may emerge from time to time, and it is not possible for Kura's management to predict all risk factors and uncertainties.

All forward-looking statements contained in this presentation speak only as of the date on which they were made. Other risks and uncertainties affecting us are described more fully in our filings with the Securities and Exchange Commission. We undertake no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.



KURA ONCOLOGY

- Clinical stage biopharmaceutical company engaged in the discovery and development of anti-cancer targeted therapies
- Sites in La Jolla, CA (Research and HQ) and Cambridge, MA (Development)



 Focused on the development of small molecules that target key cell signaling pathways and of companion diagnostics to identify patients most likely to benefit from therapy



KURA'S TWO MOST ADVANCED PROGRAMS TARGET THE MAPK PATHWAY

- The MAPK pathway includes the signaling molecules Ras, Raf, MEK, and ERK.
- Abnormal MAPK signaling may lead to:
 - increased or uncontrolled cell proliferation
 - resistance to apoptosis and
 - resistance to chemotherapy and targeted therapies



- Inhibitors of Raf and MEK have validated the MAPK pathway in cancer.
- With tipifarnib and KO-947, Kura Oncology is investigating additional methods to target abnormal MAPK signaling.



PIPELINE OF SELECTIVE DRUG CANDIDATES FOR GENETICALLY DEFINED CANCERS







* Kura Oncology holds worldwide rights in all indications excluding virology, subject to Janssen having ROFN

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TIPIFARNIB – FARNESYL TRANSFERASE INHIBITOR

- Competitive inhibitor of CAAX peptide binding site of farnesyltransferase; In-licensed from Janssen
- Extremely potent and highly selective inhibitor of farnesylation; no inhibition of GGTI
- Previously studied in > 5,000 patients (70+ studies)
- Manageable safety profile as single agent therapy
 - 472 patients with solid tumors treated with tipifarnib monotherapy with adverse events of myelosupression (neutropenia 25%, anemia 31%, thrombocytopenia 19%), fatigue (41%) and GI unspecific (nausea 47%, anorexia 33%, diarrhea and vomiting 32%) well tolerated (<25% treatment discontinuation)
- Previous efforts yielded insufficient clinical activity to support a registration; however, there was anecdotal evidence of durable single agent activity.







MECHANISM OF ACTION OF TIPIFARNIB







Tipifarnib may mediate TGI by inhibiting uniquely farnesylated proteins such as HRAS

HRAS AS A DOWNSTREAM TARGET OF FTI

100₁

90

- **HRAS** mutant tumors are more sensitive to FTIs
- % Reduction Tumor Growth 80 (final tumor weight) 70-Tumors with **60** KRAS and NRAS T24 H-ras **50** C32 ras wildtype mutations are 40 🛧 Lovo K ras-B less sensitive to 30 - Capan-2 K ras-B 20 **FTIs** 10 0

12.5

6.25

HRAS G12V

Tipifarnib (mg/kg, BID)

25

50

100

25 mg/kg BID results in <10% TGI in KRASm, 50% inhibition in RAS wt, and >80% TGI in HRASm



HRAS MUTANT SOLID TUMORS

- HRAS mutant solid tumors include urothelial cancer (~15%), salivary gland tumors (SGT) (~15%), head and neck squamous cell carcinoma (SCCHN) (~5%) and other cancers (Data from TCGA)
- HRAS is the predominantly mutated RAS species in urothelial cancer, SGT and SCCHN
 - More frequent occurrence of HRAS (3-6%) than KRAS mutation in SCCHN^{1,2}
 - More frequent association of HRAS versus KRAS mutation in the setting of tobacco exposure (chewing) in humans (up to 12% OSCC) ³ and chemical carcinogen exposure in mice ⁴



Figure from www.cancer.gov/research/keyinitiatives/ras/ras-central/blog/ras-proteins-created-equal

- 1. Anderson et al. J Otolaryngol. 1992;21:321–326
- 2. Anderson et al. Arch Otolaryngol Head Neck Surg. 1994;120:755-760
- 3. Sathyan et al. Modern Path 2007; 20, 1141-8
- 4. Saranath et al. Br J Cancer. 1991;63:573-578

ENCOURAGING PHASE 2 DATA SUPPORTS HRAS HYPOTHESIS IN HEAD AND NECK CANCER

- Trial Design
 - 36 patient study in two 18-patient cohorts, each with a Simon two-stage design
 - Cohort 1: Thyroid cancer
 - Cohort 2: Other HRAS mutant solid tumors
 - Primary Objective: ORR. 10% (H0) vs 30% (H1) ORR hypotheses
 - Regimen: 900 mg bid daily on Days 1 7 and 15 21 in 28-day cycles
 - P.I. Alan Ho MD, MSKCC
 - Urothelial carcinoma independently investigated under an IST at Samsung Medical Center (K. Park, MD)

• Preliminary Data

- Cohort 1 in HRAS mutant thyroid carcinomas still enrolling in 1st stage
- Eleven evaluable patients enrolled in 1st stage of Cohort 2
 - In 3 patients with HRAS mutant SCCHN, 2 confirmed PRs and a 7-month SD
 - In 5 evaluable patients with HRAS mutant salivary gland tumors, 3 SDs >6 mo
- Study has proceeded to 2nd stage and has been amended to enroll 7 additional patients with HRAS mutant SCCHN in cohort 2
- Tipifarnib was generally well tolerated. AEs consistent with the known safety profile of tipifarnib



KO-TIP-001 (STAGE 1): EVALUABLE SCCHN AND SGT PATIENTS*







- Why would HRAS mutant inhibition affect the progression of head and neck tumors ?
- Why would FTI translate to tumor regression in SCCHN?
- Could tipifarnib address an unmet medical need in SCCHN ?



 "A subgroup of oral cavity tumors...displays infrequent copy number alterations in conjunction with activating mutations of HRAS or PIK3CA...The three-gene constellation of wild-type TP53 with mutant HRAS and CASP8 suggested an alternative tumorigenesis pathway involving RAS and/or alterations in cell death/NF-κB^{''1}



1. Cancer Genome Atlas Research Network. Nature 2012;489:519-25



ROLE OF HRAS IN SQUAMOUS LUNG CANCER

- "Lung SqCCs share many alterations in common with head and neck squamous cell carcinomas without evidence of human papilloma virus (HPV) infection, including mutation in PIK3CA, PTEN, TP53, CDKN2A, NOTCH1 and HRAS, suggesting that the biology of these two diseases may be similar."¹
 - HRAS is the most frequently mutated RAS gene (2-3%) in squamous lung cancer²

- 1. Cancer Genome Atlas Network. Nature 517, 576–582, 2015
- 2. Liau et al. Lung Cancer Manag. 2012; 1: 293–300



HRAS MEDIATES RESISTANCE TO ANTI-EGFR THERAPY IN SCCHN

- HRAS mutations drive resistance to erlotinib and cetuximab in SCCHN cell lines ^{1,2}
- RAS-mediated **acquired resistance** to cetuximab in SCCHN patients³
 - 46% of patients with on-treatment disease progression showed acquired RAS mutations, while no RAS mutations were found in the non-progressive subset of patients.
 - 3 of 6 mutations (23% of total patients with on-treatment disease progression) were in HRAS
 - Maximum time from mutation detection to clinical progression of 16 weeks.

- 2. Hah et al. Head Neck. 2014;36:1547-54
- 3. Braig et al. Oncotarget. 2016;7(28):42988-95



^{1.} Rampias et al. Clin Cancer Res. 2014;20:2933-46

HRAS MUTANT SQUAMOUS CELL CARCINOMAS ARE RESISTANT TO CETUXIMAB BUT SENSITIVE TO TIPIFARNIB



HRAS A146P Head & Neck SCC

HRAS Q61K Lung SCC



PATIENT 005-005

- Elderly white male with a metastatic squamous head and neck cancer (primary tracheal tumor)
- Non hotspot HRAS Q22K (and an INK4 gene deletion)
 - HRAS Q22K is likely a driver mutation
 - Observed in Costello syndrome (tumor predisposition due to germline HRAS mutations)
 - Equivalent KRAS Q22K mutation known to be tumor-related ^{2,3}
 - Wild type TP53, CASP8 and PIK3CA status⁴
- Prior Therapy:
 - Cetuximab with chemotherapy for ~6 months with best response of SD
 - Disease was stable for an additional ~8 months, then progressed and the patient joined the tipifarnib trial
- Response to Tipifarnib:
 - PR at C6D22 and has been on treatment with tipifarnib for over one year, currently in C15



- 1. van der Burgt *et al. J Med Genet.* 2007 ; 44: 459–462.
- 2. Metro et al. Ecancermedicalscience. 2015; 9: 559.
- 3. Azzato et al. Anticancer Research 2015 ;35 no. 5 3007-30012
- 4. IMPACT NGS data provided by Alan Ho MD, MSKCC

005-005 CT SCANS



08/17/2015 (Baseline)



12/22/2015 (Cycle 4 Day 22)

Provided by Alan Ho, MD, MSKCC



PATIENTS 005-007 AND 005-009

- Patients 005-007 and 005-009 are two male subjects with advanced oral cavity squamous head and neck tumors that carry the HRAS hotspot mutation Q61K
 - Both patients have wild type TP53, CASP8 and PIK3CA status¹
 - Patient 005-007 presented 12 additional cancer-related mutations
- Prior to joining the tipifarnib phase 2, these patients received cetuximab either as monotherapy (005-007) or in combination with chemotherapy (005-009)
 - In both patients, treatment with cetuximab was ineffective
 - Patient 005-007 experienced a short lived disease stabilization (~3 months on cetuximab treatment)
 - Patient 005-009 experienced a best response of disease progression (~2 months on treatment)



PATIENTS 005-007 AND 005-009

- Patient 005-007
 - Experienced a disease stabilization with tipifarnib that lasted 7 months.
 - At that time, the patient left the tipifarnib study due to symptomatic deterioration (progression by imaging was not confirmed)
- Patient 005-009
 - Experienced a PR at C2D22
 - This patient has been now on study for more than 7 months and continues on treatment (C8)



CONCLUSIONS / DISCUSSION POINTS

- A subset of SCCHN appears sensitive to FTI with tipifarnib
 - Additional SCCHN patients will be enrolled in KO-TIP-001 to verify the initial findings
 - Due to the commonalities between SCCHN and SCC-NSCLC, sensitivity of SCC-NSCLC to tipifarnib might be expected
- HRAS mutant SCCHN may be refractory to anti-EGFR therapy
 - A SCCHN patient with known HRAS mutant status might benefit from receiving tipifarnib instead of anti-EGFR therapy
 - The effect of HRAS mutation on anti-PD-1/PD-L1 therapy is unknown; however, due to their overall reported ORR (13- 18%)^{1,2}, HRAS mutant tumors might continue to constitute an unmet medical need
- A SCCHN patient who had initially wild type HRAS but became refractory to anti-EGFR treatment might present a *de novo* HRAS mutation

1. Chow et al. J Clin Oncol. 2016 Sep 19. pii: JCO681478. [Epub ahead of print]

2. Ferris et al. N Engl J Med. 2016 Oct 8. [Epub ahead of print]



KO-947 – STRONG ACTIVITY IN MAPK PATHWAY MODELS WITH FLEXIBLE DOSING

Rationale:

- Aberrant signaling caused by mutations or dysregulation of the MAPK pathway associated with numerous tumor types.
- Inhibitors of Raf and MEK have validated the MAPK pathway in cancer.
- Acquired resistance to Raf and MEK inhibitors has been documented due to reactivation of ERK1/2 kinases.

Attributes of KO-947

- ATP competitive inhibitor of the extracellular receptor kinase (ERK)
- KO-947 induced tumor regression in PDX tumor models with mutations and/or dysregulation of MAPK pathway at tolerable doses.
- IV administration provides potential to improve exposure and tolerability.





KO-947 COMPARES FAVORABLY WITH CLINICAL STAGE COMPETITOR COMPOUNDS

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Compound	KO-947	GDC-0994	BVD-523
Erk Enzymatic IC ₅₀	9.7 nM	14 nM	14 nM
Kinase Selectivity	>50X vs 415 kinases	>50 fold*	>1000X vs 75 kinases**
Cellular p90RSK IC ₅₀	14 nM	179 nM	365 nM
Cellular p90RSK Wash-out (24 hrs)	54 nM	>10 uM	-
Cellular Proliferation A375 (BRAF) IC ₅₀	32 nM	272 nM	521 nM
Cellular Proliferation H358 (G12C) IC ₅₀	18 nM	464 nM	737 nM
Cellular Proliferation A375 (BRAF) IC ₅₀ Wash-out (2 washes)	230 nM	>10 uM	-

Kura Oncology data *J. Med. Chem.2016. DOI: 10.1021/acs.jmedchem.6b00389 **AACR 2015, Abstract 4693



KO-947 IS BROADLY ACTIVE AGAINST MAPK PATHWAY MUTANT CELL LINES



• KO-947 is more potent than GDC-0994 in cell lines with MAPK activating mutations



KO-947 DEMONSTRATES PROLONGED SUPPRESSION OF ERK SIGNALING



• Extended pharmacology of KO-947 supports potential for intermittent dosing schedules



Kura Oncology data

KO-947: TRANSLATIONAL RESEARCH IDENTIFIED POTENTIAL LEAD CLINICAL INDICATIONS



- Robust anti-tumor activity demonstrated in two broad tumor classes with > 50% response rates in preclinical models
- Potential biomarkers have been identified

Kura Oncology data



Evaluated KO-947 in 138 PDX models across 20 potential indications

KO-947: ADVANCEMENT TO CLINICAL TESTING



- IND-enabling studies and preparation completed/ongoing
- IV route of administration selected for clinical studies
- Potential biomarkers being characterized



- IND submission
- Initiate Phase 1 study

2H 2016 1H 2017



OVERALL CONCLUSIONS

- Although knowledge on the RAS-ERK pathway has accumulated in last 40 years, therapeutic development in this area has been limited
- Tipifarnib and KO-947 might be able to provide clinical benefit in settings of unmet medical need by linking pharmacological intervention to RAS-ERK pathway mutation/dysregulation
- Molecular characterization of tumors with RAS-ERK pathway mutation or dysregulation may facilitate the development of novel ways of therapy for these previously thought non-targetable alterations



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- Carrie Melvin, David Wages and the KO-TIP-001 Study Team
- Francis Burrows, Dana Hu-Lowe, Yi Liu and the KO-947 Project Team
- Our patients and their families





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