Inhibiting K-RAS in the Clinic – Are we There yet?

Alex A. Adjei

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SWOG Translational Science Symposium
Chicago, IL
RAS signaling is evolutionally conserved across species

**Mammals**
- RTK
- Grb2
- SOS
- Ras
- Raf
- MEK
- ERK
- Growth

**Drosophila**
- Sev
- Drk
- sos
- Dras1
- D-Raf
- DSOR1
- ROLLED
- Eye Development

**C. elegans**
- Let-23
- Sem-5
- Sos1
- Let-60
- Lin-45
- Mek-2
- MPK-1
- Vulva Development
Ras is the most mutated oncogene in Cancer

- 32% of all human cancers have Ras missense mutations

<table>
<thead>
<tr>
<th>GENE</th>
<th>%*</th>
<th>H-Ras</th>
<th>N-Ras</th>
<th>K-Ras 4A</th>
<th>K-Ras 4B</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRAS</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRAS</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- H-Ras
- N-Ras
- K-Ras 4A
- K-Ras 4B

COSMIC:
- Pancreatic: 90% KRAS
- Colorectal: 50% KRAS
- Lung: 30% KRAS
- Melanoma: 25% NRAS
Ras activates MAP kinase via a phosphorylation cascade that proceeds from Ras to Raf kinase, to MEK kinase, and finally to MAP kinase. MAP kinase then dimerizes and enters the nucleus.
Mutant Ras is GAP-insensitive and persistently GTP-bound

Transient activation by extracellular stimuli

GTP → GEF → GDP

“Off”

“On”

Ras GDP

GDP

Ras

GTP

GAP

E

Normal cell

Chronically GTP-bound and activated, persistent deregulated signaling

GTP → GDP

GTP

Ras

GDP

GTP

GAP

E

Cancer cell

*G12, G13, Q61

Mutant Ras is GAP-insensitive and persistently GTP-bound
Ras binds GTP with pM affinity: Difficult to disrupt

\[
K_d = 4.6 \text{ nM} \\
K_m = 148 \text{ µM} \\
K_d = 60 \text{ pM}
\]


Feuerstein et al (1987) JBC 262:8455
Anti-K-Ras strategies

- Direct inhibitors of Ras-GTP
- Inhibitors of plasma membrane association
- Inhibitors of downstream effector signaling
- Synthetic lethal partners
- RNAi

K-Ras4B
Inhibitors of Ras membrane association: the farnesyltransferase inhibitors (FTIs)

Membrane-bound, active

Cytoplasmic, inactive

\[ \text{C15 farnesyl isoprenoid} \]
FTIs Reverse the Malignant Phenotype

- Control
- H-Ras Transformed
- H-Ras Transformed + FTI
FTIs Cure H-ras mutant Tumor-Bearing Mice

Inhibition of farnesyltransferase induces regression of mammary and salivary carcinomas in ras transgenic mice

FTIs (Tipifarnib, Lonafarnib) Negative Pivotal trials

- Pancreatic Cancer
- Non-small Cell Lung Cancer
- Colorectal Cancer
- Acute Myelogenous Leukemia
Admit it .... you feel like doing this to someone everyday.
K-Ras and N-Ras undergo FTI-induced alternative prenylation

Only H-Ras is FTI-inhibited

- C-OMe
- CAAX

K-Ras

Ras

Icmt

Rce1

FTI

FTase

GGTase-I

= C15 farnesyl isoprenoid
= C20 geranylgeranyl isoprenoid

NRAS 12%
HRAS 3%
KRAS 85%
Efforts have focused on “indirect” inhibition of Ras Downstream Signaling
KRAS G12 mutations are the most frequent in different cancers

- **PDAC**: 99%
- **CRC**: 78%
- **NSCLC**: 91%

- G12: <1%
- G13: 20%
- Q61: 6%
- A146: 91%
- Other: 6%
KRAS G12 mutation frequencies in different cancers may provide a role for mutation-specific therapies

RAS mutations and oncogenesis: Miller & Miller (2011) Front Genet 2:100
Approach to inhibiting KRAS G12C

**The KRAS Binding Problem**

- The KRAS GTP pocket is inaccessible due to high affinity for GTP
- GTP binds and activates KRAS
- KRAS tumor survival signaling

**The KRAS G12C Opportunity**

1. KRAS G12C has a **cysteine** present in its inactive form
2. Binding to the cysteine opens an adjacent Switch II pocket
3. Inhibitor covalently binds to the cysteine and the induced Switch II pocket
4. KRAS G12C is irreversibly locked in the **inactive state**

KRAS tumor survival signaling is halted

Janes et al., 2018, Cell 172, 578–589
KRAS dependency in vitro to in vivo

Tumor

3D

2D

Active state KRAS-GTP

Accumulation of ARS-1620 modified GDP-bound KRAS^{G12C}

Covalent KRAS^{G12C} inhibitor

ARS-1620

LC/MS-MS

RAS signaling

G12C-directed target suppression in vivo

Mutant G12C Precision in vitro

Transcriptome profile

Proteomic cysteine profile

Cysteine Targets

ARS-1620

ARS-1620

Selectively Efficacy in KRAS^{G12C} tumor models
Janes et al., 2018, Cell 172, 578–589
Covalent Inhibitors of KRAS G12C in the clinic

• AMG 510 (NCT03600883)
• MRTX 849 (NCT03785249)
• JNJ-74699157 (NCT04006301)
Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics (PK) and Efficacy of AMG 510, a Novel Small Molecule KRAS$^{G12C}$ Inhibitor, in Advanced Solid Tumors

Marwan G Fakhri, MD; Bert Howard O’Neil, MD; Timothy J Price, MBBS, FRACP; Gerald S Falchuk, MD; Jayesh Desai, MBBS, FRACP; James Kuo, MBBS, FRACP; Ramaswamy Govindan, MD; Erik Rasmussen, MS; Phuong Khanh Morrow, MD; Jude Ngang, PharmD; Haby Henary, MD; David Hong, MD

1City of Hope, Duarte, CA, USA; 2Indiana University, Simon Cancer Center, Indianapolis, IN, USA; 3The Queen Elizabeth Hospital, Woodville South, AU; 4Amgen Inc, Thousand Oaks, CA, USA; 5Sarah Cannon Research Institute, Denver, CO, USA; 6Peter MacCallum Cancer Centre, Melbourne, AU; 7Scientia Clinical Research, Randwick, AU; 8Washington University, St Louis, MO, USA; 9MD Anderson Cancer Center, Houston, TX, USA
Proportion of G12C and non G12C mutations in selected cancers

- 13% of NSCLC, 3% of CRC & appendix cancer, and 1%–3% of other solid tumors
AMG 510 is a First-in-Class KRAS\textsuperscript{G12C} Inhibitor

- AMG 510 specifically and irreversibly inhibits KRAS\textsuperscript{G12C} by permanently locking it in an inactive GDP-bound state.

AMG 510 First-in-Human Study Design

**Phase 1, Multicenter, Open-label Study – Dose Escalation**

- **Key Eligibility**
  - Locally advanced or metastatic malignancy
  - Received prior standard therapies
  - KRAS G12C mutation as assessed by molecular testing of tumor biopsies
  - No active brain metastases

- 2–4 patients enrolled in each cohort
- Intra-patient dose escalation allowed
- Additional patients may be added to any dose deemed safe

- **Cohort 1**
  - 180 mg
- **Cohort 2**
  - 360 mg
- **Cohort 3**
  - 720 mg
- **Cohort 4**
  - 960 mg

- Repeated oral daily dosing with 21-day cycles
- Treatment until disease progression, intolerance, or consent withdrawal
- Radiographic scan every 6 weeks

**Primary endpoints:**
- Dose-limiting toxicities; safety

**Key secondary endpoints:**
- PK; objective response rate; duration of response; disease control rate; PFS; duration of stable disease

*30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long-term follow-up. PK: pharmacokinetics; PFS: progression-free survival.

**Dose Expansion**

- Patients with KRASG12C mutant advanced tumors
  - N = ~20 (max 60)
AMG 510 Pharmacokinetic Profile - 960 mg PO Dose (n=9*)

<table>
<thead>
<tr>
<th>Geometric Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (µg/mL)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24h}$ (hr*µg/mL)</td>
</tr>
<tr>
<td>$t_{1/2,z}$ (hr)</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>7.84 (8.09)</td>
</tr>
<tr>
<td>140 (117)</td>
</tr>
<tr>
<td>6.5 (range: 4.2-8.0)</td>
</tr>
</tbody>
</table>

IC90 in 2 hour cellular pERK assay

*PK data cutoff 12 April 2019
Duration of Treatment by Tumor Types and Responses (n=29)

Duration on Treatment (as of 4 April 2019)
- NSCLC Partial Response (n=5): 7.3 – 27.4 weeks
- Stable Disease (n=4): 8.4 – 25.1 weeks
- CRC/Other Stable Disease (n=14): 7.3 – 24.0 weeks

- ▲ First Response
- • Best Overall Response: PR: 5, SD: 18, PD: 6
- □ Disease Progression: 9
- ▮ Ongoing on-study: 20

* Appendix adenocarcinoma patient
SD → PD: Patient with best response of SD but who later progressed

Presented at: 2019 ASCO Annual Meeting
#ASCO19
Presented by: Marwan G. Fakhri, MD

©2016 MFMER, slide 26
CRC: Individual Patient Radiologic Response and Biomarkers

Demographics:
34 y.o. Female, diagnosed with metastatic colon adenocarcinoma April 2014

Treatment history:
- FOLFOX and HIPEC in Aug 2015, followed by FOLFOX until Dec 2015
- FOLFiRI with PD in Aug 2016
- HIPEC Oct 2016
- Capecitabine + bevacizumab Aug 2017
- Phase I clinical trial March-June 2018
- AMG 510 - 360 mg since Oct 2018

Response:
- Biochemical response (normal CEA)
- SD (-18% local read), still on treatment (22.3 weeks as of data cutoff)
CRC and Other Solid Tumors: Best Tumor Response* (n=19)

* Based on local radiographic scans every 6 weeks using RESIST 1.1 criteria
1 CRC patient progressed prior to week 6 and is not on this graph
1 appendix patient had clinically stable disease but is not shown on this graph

Presented By Marwan Fakih at 2019 ASCO Annual Meeting
CRC Cohort : Update at ESMO

• 12 pts treated at RP2D
• 1 PR (8%)
• 10 SD
• DCR (92%)
Phase 1 Study of Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510, a Novel KRASG12C Inhibitor, in Non-Small Cell Lung Cancer

Ramaswamy Govindan, MD;1 Marwan G Fakih, MD;2 Timothy J Price, MBBS, DHIthSci, FRACP;3 Gerald S Falchook, MD;4 Jayesh Desai, MBBS, FRACP;5 James C Kuo, MBBS, FRACP;6 John H Strickler, MD;7 John C Krauss, MD;8 Bob T Li, MD;9 Crystal S Denlinger, MD;10 Greg Durm, MD;11 Jude Ngang, PharmD;12 Haby Henary, MD;12 Gataree Ngarmachmanrith, MD;12 June Kim, PhD;12 Phuong Khanh Morrow, MD;12 David S Hong, MD13

1Alvin J Siteman Cancer Center at Washington University School of Medicine, St Louis, MO, USA; 2City of Hope, Duarte, CA, USA; 3The Queen Elizabeth Hospital, Woodville South, Australia; 4Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; 5Peter MacCallum Cancer Centre, Melbourne, Australia; 6Scientia Clinical Research, Randwick, Australia; 7Duke University Medical Center, Durham, NC, USA; 8University of Michigan, Ann Arbor, MI, USA; 9Memorial Sloan Kettering Cancer Center, New York, NY, USA; 10Fox Chase Cancer Center, Philadelphia, PA, USA; 11Indiana University, Simon Cancer Center, Indianapolis, IN, USA; 12Amgen Inc., Thousand Oaks, CA, USA; 13MD Anderson Cancer Center, Houston, TX, USA
**Patient Disposition**

**Overall Trial Accrual**

- **N = 76** Total patients enrolled
  - NSCLC, N = 34
  - CRC, N = 36
  - SCLC, N = 1\(^a\)
  - Appendiceal cancer, N = 3
  - Endometrial cancer, N = 1
  - Small bowel cancer, N = 1

- **N = 34** NSCLC patients enrolled
  - N = 19, escalation cohort
    - 180 mg: N = 3
    - 360 mg: N = 2
    - 720 mg: N = 6
    - 960 mg: N = 8
  - N = 15, expansion cohort
    - 960 mg: N = 15

- **N = 23**, evaluable
  - Patients who had the first 6-week scan or early progressive disease

- **N = 4**, discontinued study\(^b\)
  - None was related to treatment

**First patient enrolled**: 27 August 2018

**Data cutoff**: 17 July 2019
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>N = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) – years</td>
<td>67.5 (49.0–77.0)</td>
</tr>
<tr>
<td>Female – n (%)</td>
<td>18 (52.9)</td>
</tr>
<tr>
<td>ECOG performance status score – n (%)</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>0</td>
<td>26 (76.5)</td>
</tr>
<tr>
<td>1</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Prior lines of systemic anticancer therapy – n (%)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>1</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>2</td>
<td>29 (85.3)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td></td>
</tr>
<tr>
<td>No. of prior systemic anticancer therapy – median (range)</td>
<td>3.5 (1–8)</td>
</tr>
</tbody>
</table>
### Patient Incidence of Adverse Events (AEs): Summary

<table>
<thead>
<tr>
<th></th>
<th>All AEs N = 34 n (%)</th>
<th>All treatment-related AEs N = 34 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade ≥ 2</td>
<td>26 (76.5)</td>
<td>12 (35.3)</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>20 (58.8)</td>
<td>8 (23.5)</td>
</tr>
<tr>
<td>Grade ≥ 4</td>
<td>11 (32.4)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td></td>
<td>5 (14.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dose-limiting toxicity</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>8 (23.5)</td>
<td>0 (0)b</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>4 (11.8)a</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

- No dose-limiting toxicities were reported
- No treatment-related serious or fatal AEs were reported
- There were no AEs leading to treatment discontinuation

- **960 mg oral daily dose** was identified as the expansion dose and recommended phase 2 dose
### Patient Incidence of Treatment-Related Adverse Events (AEs)

<table>
<thead>
<tr>
<th>All Treatment-Related AEs</th>
<th>Any Grade N = 34, n (%)</th>
<th>Grade 3 N = 34, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related AEs</td>
<td>12 (35.3)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (11.8)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (5.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>2 (5.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (5.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Blood alkaline phosphate increased</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All Treatment-Related AEs</th>
<th>Any Grade N = 34, n (%)</th>
<th>Grade 3 N = 34, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (2.9)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*ALT: alanine aminotransferase; AST: aspartate aminotransferase; AE: adverse event.*

- 12 of 34 patients (35.3%) reported treatment-related AEs; most were grade 1 or 2.
- 3 of 34 patients (8.8%) reported two grade 3 treatment-related AEs: diarrhea and anemia.
- There were no grade 4 or higher treatment-related AEs.
NSCLC: Individual Patient Radiologic Responses

**Demographics:**
61 y.o. Female, diagnosed with KRAS$^{G12C}$ metastatic NSCLC
August 2010

**Treatment history:**
- Radiation + Carboplatin/Taxol from Aug 2010 until Oct 2010
- Carboplatin/Pemetrexed from Oct 2016 until Jun 2017
- Nivolumab from Aug 2017 until Apr 2018
- AMG 510 – 180 mg since Sept 2018

**Best Response:**
- PR (-34% central read) Still on treatment (27.4 weeks as of data cutoff)

**Demographics:**
59 y.o. Male, with KRAS$^{G12C}$ metastatic NSCLC, December 2013

**Treatment history:**
- Carboplatin/Pemetrexed Feb 2014 until Feb 2015
- Erlotinib from April 2015 until Jun 2015
- Nivolumab Aug 2015 until Aug 2017
- Dasatinib from Jul 2016 until Aug 2017
- M3541 (Targeted biologic) from Oct 2017 until Nov 2017
- AMG 510 - 360 mg since Dec 2018

**Best Response:**
- PR (-67% central read) Still on treatment (14.3 weeks as of data cutoff)
- CR to the targeted lesions were reported at week 18 (post data cutoff)
Best Tumor Response and Change in Tumor Burden From Baseline

Efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>All evaluable patients N = 23</th>
<th>Evaluable patients treated with 960mg N = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response – n (%)</td>
<td>11 (48)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Stable disease – n (%)</td>
<td>11 (48)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Progressive disease – n (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Objective response rate – %</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>Disease control rateb – %</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>

*One patient discontinued study due to PD prior to the 1st assessment, and the post-baseline tumor burden data are missing. *PR or SD at week 6. *Patient had complete response to the target lesions. Evaluable patients: patients who had the first 6-week scan or early PD. NSCLC: non-small cell lung cancer; PR: partial response; SD: stable disease; PD: progressive disease.

**Study ongoing**

**Confirmed response**
Time to Response and Duration of Treatment for All Dose Levels

- **Evaluable NSCLC Patients, N = 23**
- **Patients With PR, N = 11**
- **Patients With SD, N = 11**

- **First response (PR or better)**
- **Best overall response**
- **Disease progression**
- **Study ongoing**
- **Death**

**Planned dose:**
- 180 mg
- 360 mg
- 720 mg
- 960 mg

**Duration of Treatment (Weeks)**

- Median (range) duration of treatment – weeks
  - Patients With PR: 15.1 (4.1–42.3)
  - 8/11 patients continuing study
Efficacy of AMG 510 Administered at 960 mg, the Recommended Phase 2 Dose

Efficacy with 960 mg

<table>
<thead>
<tr>
<th>Best overall response</th>
</tr>
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<tbody>
<tr>
<td>Partial response – n (%)</td>
</tr>
<tr>
<td>Stable disease – n (%)</td>
</tr>
<tr>
<td>Progressive disease – n (%)</td>
</tr>
</tbody>
</table>

Objective response rate – % | 54

Disease control rate* – % | 100

*PR or SD at week 6. Evaluable patients: patients who had the first 6-week scan or early progressive disease; PR: partial response; SD: stable disease.
AMG 510 Updates

• Expansion cohorts ongoing
• Combination with Trametinib
• Combination with AMG 404
• Other Combinations
• Ongoing preclinical studies aimed at inhibiting G12D tumors
Inhibiting Kras in the Clinic

We are almost there..........
THANKS!

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