Targeting Molecular Pathways in the Clinic – $K$-RAS as an example

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Agenda

• Prognostic and Predictive Value

• Recent clinical trials targeting K-RAS muts

• Bench to Bedside Approaches
Mutational Activation of the K-ras Oncogene

Sjoerd Rodenhuis, M.D., Marcus L. van de Wetering, B.S., Wolter J. Mooi, M.D., Siegina G. Evers, B.S., Nico van Zandwijk, M.D., and Johannes L. Bos, Ph.D.

Molecular Changes Driving Lung Adenocarcinoma

No mutation detected

- KRAS 25%
- EGFR 17%
- EML4-ALK 7%
- Double 3%
- Other mutations

Prognostic Significance of KRAS Mutation in NSCLC
Prognostic Significance of *KRAS* mutation

**Slebos NEJM 323: 561, 1990**

- Disease-free Survival
  - No mutation: Solid line
  - Mutation: Dotted line

- Overall Survival
  - No mutation: Solid line
  - Mutation: Dotted line

**Tsao JCO 25:5240, 2007**

- JBR.10
  - HR 1.23, p=0.40
  - N=113

**Schiller. J Clin Oncol 19: 448, 2001**

- ECOG 4592
  - HR 0.82, P=0.38
  - N=44
No prognostic effect of *KRAS* mutations in the LACE-Bio pooled analysis

All Patients

The Spectrum of Ras Mutations

![Pie charts showing the distribution of mutations in HRAS, KRAS, and NRAS](chart.png)
LACE-Bio: KRAS Mutation Type

Patients with KRAS status
N = 1543

KRAS Wild-type
N = 1243

KRAS mutated
N = 300*

Codon 12
N = 275†

G12C or G12V
N = 209

G12D or G12S
N = 41

G12A or G12R
N = 22

Codon 13
N = 24

* One codon 14 mutation, 3 double mutations on codon 12
Prognostic Effect of KRAS Codon 12 & 13 Mutations on OS

Logrank p = 0.83

- KRAS WT
- Codon 12 mut (1.04)
- Codon 13 mut (1.01)
- p = 0.96

Shepherd et al. Proc ASCO, 2012
K-Ras dependent and independent cell lines
OS according to K-RAS mutation and gene expression in T1 NSCLC

\[ K = 2 \]

\[ K = 3 \]

VUMc - unpublished
Predictive Value of KRAS

Chemotherapy
K-RASt mutations have no predictive value for platinum based chemotherapy in NSCLC

Differential sensitivity of *K-RAS* mutated NSCLC for standard chemotherapy regimen

Mellema et al. In press
Which is restricted to G12V K-RAS mutations
G12V and G12C *K-Ras* mutations confer sensitivity to treatment with selumetinib and docetaxel

Not all *K-Ras* is created equal. Secondary analysis from BATTLE

KRAS as Therapeutic Target

MET Inhibition
RAF Inhibition
MEK Inhibitors
## Tivantinib (ARQ 197): PFS in Histologic and Molecular Subgroups

<table>
<thead>
<tr>
<th></th>
<th>ARQ197/erlotinib</th>
<th>Placebo/erlotinib</th>
<th>Unadjusted HR</th>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>Median PFS (95% CI, months)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Squamous Cell</td>
<td>26/24</td>
<td>3.2 1.9-4.2</td>
<td>2.0 1.8-4.9</td>
</tr>
<tr>
<td>Non-Squamous Cell</td>
<td>58/59</td>
<td>4.4 3.5-7.3</td>
<td>2.3 1.9-3.7</td>
</tr>
<tr>
<td>c-MET FISH &gt;4</td>
<td>19/18</td>
<td>3.6 1.9-5.7</td>
<td>3.6 1.7-3.8</td>
</tr>
<tr>
<td>c-MET FISH &gt;5</td>
<td>8/11</td>
<td>5.6 3.8-NE</td>
<td>3.6 1.8-7.3</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>6/11</td>
<td>5.6 1.9-7.5</td>
<td>4.9 1.9-8.4</td>
</tr>
<tr>
<td>EGFR wt</td>
<td>51/48</td>
<td>3.2 1.9-4.2</td>
<td>1.9 1.8-2.3</td>
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<tr>
<td>KRAS mutant</td>
<td>10/5</td>
<td>2.3 1.8-NE</td>
<td>1.0 0.3-1.9</td>
</tr>
<tr>
<td>KRAS wt</td>
<td>49/45</td>
<td>3.6 1.9-4.2</td>
<td>2.3 1.9-3.7</td>
</tr>
</tbody>
</table>

Sequist et al. ESMO 2010
### MARQUEE: OS in Key Subgroups

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group</th>
<th>N</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>All</td>
<td>All</td>
<td>1048</td>
<td>.98 (.84-1.15)</td>
</tr>
<tr>
<td>EGFR</td>
<td>Mutant</td>
<td>109</td>
<td>.72 (.35-1.48)</td>
</tr>
<tr>
<td></td>
<td>Non-Mutant</td>
<td>937</td>
<td>1.00 (.85-1.18)</td>
</tr>
<tr>
<td>KRAS</td>
<td>Mutant</td>
<td>284</td>
<td>1.04 (.78-1.40)</td>
</tr>
<tr>
<td></td>
<td>Non-Mutant</td>
<td>702</td>
<td>.94 (.77-1.14)</td>
</tr>
<tr>
<td></td>
<td>Indeterminate</td>
<td>62</td>
<td>1.46 (.69-3.07)</td>
</tr>
<tr>
<td>MET</td>
<td>High</td>
<td>211</td>
<td>.70 (.49-1.01)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>234</td>
<td>.90 (.64-1.26)</td>
</tr>
<tr>
<td></td>
<td>Not Assessable</td>
<td>603</td>
<td>1.13 (.92-1.39)</td>
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<tr>
<td>ECOG PS</td>
<td>0</td>
<td>336</td>
<td>.78 (.57-1.07)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>710</td>
<td>1.10 (.91-1.32)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;65</td>
<td>646</td>
<td>.84 (.69-1.03)</td>
</tr>
<tr>
<td></td>
<td>&gt;=65</td>
<td>402</td>
<td>1.27 (.98-1.64)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>429</td>
<td>.87 (.68-1.13)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>619</td>
<td>1.06 (.86-1.29)</td>
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<tr>
<td>Prior Regimens</td>
<td>1</td>
<td>694</td>
<td>.95 (.78-1.16)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>354</td>
<td>1.03 (.79-1.34)</td>
</tr>
</tbody>
</table>

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Scagliotti et al., ECCO 2013
c-Raf, but Not B-Raf, Is Essential for Development of K-Ras Oncogene-Driven Non-Small Cell Lung Carcinoma

Rafael B. Blasco,1,6 Sarah Francoz,1,6 David Santamaría,1 Marta Cañamero,2 Pierre Dubus,3 Jean Charron,4 Manuela Baccarini,5 and Mariano Barbacid1,7
Sorafenib in *K-RAS* mut NSCLC
Overall Survival

Median OS: 5.3 months (95% CI: 3.5-6.9)

MISSION OS and KRAS mutation status

Pts with KRAS mut (in tumor or plasma)
- Sorafenib N=34; Placebo N=34
- HR=0.76 (95% CI 0.45, 1.26)
- P-value=0.279
- Sorafenib median OS= 6.4 mo (195d)
- Placebo median OS= 5.1 mo (156d)

Pts with KRAS wt
- Sorafenib N=132; Placebo N=147
- HR=0.79 (95% CI 0.6, 1.03)
- P-value=0.079
- Sorafenib median OS= 11.0 mo (339d)
- Placebo median OS= 9.1 mo (278d)

Biomarker*treatment interaction analysis: p-value=0.743
MEKi in *K-RAS* mutated NSCLC

![Diagram of MEK pathway]

- RTK
- Ras
- A-Raf
- B-Raf
- c-Raf
- MEKI
- MEK
- ERK
- Cell Proliferation

**Graph:**
- Preliminary RR is 41% (95% CI, 23-61%)
- Subjects:
  - Complete response
  - Stable disease
  - Partial response
  - Progressive disease

**Chart:**
- Maximum % Reduction from Baseline
RPhII of Trametinib vs Docetaxel in $K$-$RAS$ mut NSCLC: PFS

Blumenschein et al. Ann. Oncol. in press
Phase II, double-blind, randomized, placebo-controlled, multicenter trial; NCT00890825

**Patients**
- Locally advanced or metastatic NSCLC (stage IIIB-IV)
- Failed first-line therapy
- Confirmed KRAS mutant tumor*
- WHO PS 0-1
- Excluding symptomatic brain metastases

**Endpoints**
- Primary
  - OS
- Secondary
  - PFS
  - ORR
  - Duration of response
  - Change in tumor size
  - Alive and progression-free at 6 months
  - Safety and tolerability

**Randomization** (1:1 ratio)

**Selumetinib 75 mg BID + docetaxel 75 mg/m²**

**Placebo BID + docetaxel 75 mg/m²**

- Docetaxel was administered every 21 days; selumetinib/placebo administered daily
- Following completion of patient enrollment, the primary endpoint was changed from PFS to OS, without changing the sample size‡
  - OS analysis was planned for after approximately 58 events; HR 0.57, 80% power assuming a 1-sided 10% significance level
Docetaxel +/- Selumetinib in KRAS (+) NSCLC

Bench to Bedside approaches

Sorafenib and Metformin

*MEKi and PanHERi*
Biological systems

- Component multiplicity
- Rich connectivity
- Fail safe functioning
Sorafenib synergizes with metformin through AMPK pathway activation.

Post hoc analysis

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th></th>
<th></th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>0.01</td>
</tr>
<tr>
<td>Stable disease</td>
<td>22</td>
<td>3</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>27</td>
<td>0</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>5</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>
Phase II study Sorafenib and Metformine in K-RAS mutated NSCLC: Results

- July 2012 - June 2013 (4 centers): 55 patients

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>N (%)</th>
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</thead>
<tbody>
<tr>
<td>Median age (SD)</td>
<td>59(±10)</td>
</tr>
<tr>
<td>Sex</td>
<td>27 (49%) / 28 (51%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>16(29%) / 36(65%) / 1(2%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adeno carcinoma</td>
<td>51 (93%)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>55 (100%)</td>
</tr>
</tbody>
</table>

Mellema et al. Submitted
## Results: Response and Overall Survival

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>30 (56%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22 (41%)</td>
</tr>
<tr>
<td>Total</td>
<td>55 (100%)</td>
</tr>
</tbody>
</table>

![OS in months](image)

Mellema et al. Submitted
MEK inhibition causes upregulation of HER-2 and HER-3 in KRASm tumors

Upregulation expression and activity of HER-2 en HER-3

Pan-HER inhibitor

Growth factor

Cell membrane

MEK-inhibitor

C-MYC

RAS

RAF

MEK

ERK

PI3K

AKT

mTOR

PTEN

Gene expression

Proliferation

Cell death

Cell survival (anti-apoptosis)

Angiogenesis

Sun et al. Cell Reports 7; 1-10; 2014
MEK inhibition causes upregulation of HER-2 and HER-3 in KRASm tumor in vivo

MEKi plus pan-HERi-based combination strategies for patients with KRASm tumors

<table>
<thead>
<tr>
<th>Pan-HERi</th>
<th>+ MEKi</th>
<th>Clinicaltrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>dacomitinib</td>
<td>PD-0325901</td>
<td>NCT02039336</td>
</tr>
<tr>
<td>lapatinib</td>
<td>trametinib</td>
<td>NCT02230553</td>
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</tbody>
</table>
Clinical phase I/II study

Multi-center open-label proof of concept study consisting of two parts

**PART A (Phase I)**
Patients with advanced KRAS mutation positive CRC, NSCLC or pancreatic cancer
n ~ 20-30

Molecular pre-screening

Dacomitinib + PD-0325901 → RP2D
Preliminary results - Clinical activity
CEA tumor marker & time on treatment

- PR or SD on study
- PD off study
Take Home Messages

• There is no such thing as a \textit{K-RAS} mutation.

• These mutations have no prognostic value

• These mutations have no predictive value

• Combination therapy targeting \textit{K-RAS} pathway are key to improve therapeutic results.