Expanding the reach of precision oncology by drugging all KRAS mutants

AACR Meet the Expert Session
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Boehringer Ingelheim
Disclosure Statement

I am an employee of Boehringer Ingelheim RCV GmbH & Co KG

I will not discuss off-label use and/or investigational use in my presentation
Advancing precision cancer therapies

Addiction to Oncogenes—the Achilles Heal of Cancer

I. Bernard Weinstein

www.sciencemag.org  SCIENCE  VOL 297  5 JULY 2002

REVIEW

Cancer Genome Landscapes

Bert Vogelstein, Nickolas Papadopoulos, Victor E. Velculescu, Shibin Zhou, Luis A. Diaz Jr., Kenneth W. Kinzler*

Is genome-guided cancer treatment hyped?

New tailored therapies can work wonders, but the pace of development is slow

A lucky few

SCIENCE 2018; 360: 365
## Precision cancer therapies in 2021

<table>
<thead>
<tr>
<th>Target</th>
<th>Cancer types</th>
<th>Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK fusion</td>
<td>NSCLC adeno, ALCI</td>
<td>crizotinib, alectinib, ceritinib, brigatinib, lorlatinib</td>
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<tr>
<td>BCR-ABL fusion</td>
<td>CML, Ph+ ALL</td>
<td>imatinib, dasatinib, nilotinib, bosutinib, ponatinib</td>
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<tr>
<td>BRAF V600E mutation</td>
<td>Malignoma, hairy cell leukemia, NSCLC adeno, anaplastic thyroid, colorectal</td>
<td>vemurafenib, dabrafenib, encorafenib (+MEK), +EGFRi in CRC</td>
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<tr>
<td>BRCA mutation</td>
<td>Breast, epith. ovarian, fal. tube, peritoneal, prostate, pancreatic cancer</td>
<td>olaparib, rucaparib, talazoparib, niraparib</td>
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<td>EGFR del19/L858R mutation</td>
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<td>gefitinib, erlotinib, afatinib, osimertinib, dacomitinib</td>
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<tr>
<td>EGFR T790M mutation</td>
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<td>osimertinib</td>
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<td>Ezh2 mutation</td>
<td>Follicular lymphoma, epithelioid sarcoma</td>
<td>lazenthalotin</td>
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<td>FGFR2 fusion</td>
<td>Cholangiocarcinoma</td>
<td>pemigatinib</td>
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<tr>
<td>FGFR2/3 mutation or fusion</td>
<td>Bladder cancer</td>
<td>erdafitinib</td>
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<tr>
<td>FLT3 mutation</td>
<td>AML</td>
<td>midostaurin, giltertinib</td>
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<td>HER2 amplification</td>
<td>Breast cancer, gastric cancer</td>
<td>trastuzumab, pertuzumab, ado-trastuzumab emtansine, lapatinib, neratinib, margetuxumab-cmkb, fam-trastuzumab-durvalumab-m-k, trastuzumab</td>
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<tr>
<td>IDH1 mutant</td>
<td>AML</td>
<td>ivosidenib</td>
</tr>
<tr>
<td>IDH2 mutant</td>
<td>AML</td>
<td>enasidenib</td>
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<tr>
<td>KIT/PDGFR mutation</td>
<td>GIST, MDS</td>
<td>imatinib, nilotinib</td>
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<td>MET exon 14 mutation</td>
<td>NSCLC adeno</td>
<td>capmatinib, tepotinib</td>
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<tr>
<td>NF1 mutation</td>
<td>Neurofibromatosis type 1</td>
<td>selumetinib</td>
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<tr>
<td>NTRK fusion</td>
<td>NSCLC adeno, other (agnostic)</td>
<td>larotrectinib, entrectinib</td>
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<tr>
<td>PIK3CA mutation</td>
<td>ER/PR+, HER2- breast cancer</td>
<td>alpelisib</td>
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<tr>
<td>PDGFRA exon 18 mutation</td>
<td>GIST</td>
<td>avapritinib</td>
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<tr>
<td>RET fusion</td>
<td>NSCLC adeno, papillary thyroid cancer</td>
<td>seipelcratinib, pralsetinib</td>
</tr>
<tr>
<td>ROS1 fusion</td>
<td>NSCLC adeno</td>
<td>crizotinib, entrectinib</td>
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</table>
Current reach of precision oncology

• How many cancer patients can be matched with FDA-approved drugs based on mutations in their tumor’s genome?

• Prevalences are based on
  – AACR Project GENIE (release 9.0-public)
  – Literature search (eg, ER/PR+ HER2- breast cancer)

• Newly diagnosed patient numbers based on ACS Cancer Facts & Figures: Total of 1,806,590 estimated new cases in 2020

• A total of 256,000 newly diagnosed cancer patients/year (14.2%) in the US eligible for treatment by FDA-approved genome-driven therapies

• Top 6 populations: PIK3CA (ER/PR+BC), BRCA1/2, ERBB2, BRAF, EGFR, FGFR2/3
Roadblocks to drugging “Cancer’s Big Four”

- Successful targeting of “Cancer’s Big Four” will address huge patient populations
- Progress in targeting KRAS: How big is the impact?
KRAS drives cancers across different tumor types

- 186,500 newly diagnosed cancer patients/year in the US with KRAS\textsuperscript{mut}, KRAS\textsuperscript{amp}, KRAS\textsuperscript{mut+amp} in 10 cancer types with the highest total patient numbers
- With the addition of all tumor types ~ 200,000 KRAS altered cancers/year in US, close to number of patients eligible for current genome-driven therapies
- Targeting KRAS will increase genome-driven therapies from 14.2% to 25.2% (1 out of 4 cancer patients)

(1) Only samples with complete mutation and copy number profiling for KRAS are included.
(2) Calculated using tumor mutation frequencies from GENIE 9.0-public, accessed on 2021-04-07 and scaled to estimated patient numbers using cancer incidences for 2020 from ACS Cancer Facts and Figures 2020 (LUAD, 40% of Lung and Bronchus cases; IDC, 80% of Breast cases; LUSC, 20% of Lung and Bronchus cases).
KRAS alleles across cancer types

- KRAS allelic distribution varies across 7 listed tumor types shown, with almost 20,000 new KRAS G12C diagnoses per year in the US
- The top 3 KRAS alleles (G12D, G12V, G12C) accumulate to almost 110,000 new diagnoses
- While some indications are mainly driven by KRAS mutations, others such as IDC or esophageal cancer show a high level of KRASWT amplifications

CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma; LUAD, lung adenocarcinoma; UEC, uterine endometrioid carcinoma; breast invasive ductal carcinoma (IDC); STAD, stomach adenocarcinoma; ESCA/GEJC, esophageal and gastroesophageal junction cancer

Total of 174,091 KRAS-addicted tumors shown
Analysis restricted to samples with either single KRAS mutation and amplification event; very small fraction of multiple-altered samples excluded. Only samples with complete mutation and copy number profiling for KRAS are included.

Calculated using tumor mutation frequencies from GENIE 9.0-public, accessed on 2021-04-07 and scaled to estimated patient numbers using cancer incidences for 2020 from ACS Cancer Facts and Figures 2020 (LUAD, 40% of Lung and Bronchus cases; IDC, 80% of Breast cases).

**KRAS\textsuperscript{G12C}: A validated target in NSCLC**

**KRAS\textsuperscript{G12C} representation:**
- 14% of all KRAS mutations
  - 13% of lung adenocarcinomas
  - 3% of colorectal cancers
  - 1% of pancreatic adenocarcinomas

Based on 112,935 samples with mutational profiles (AACR GENIE v9.0-public)

**KRAS\textsuperscript{G12C} inhibitors – current status in ≥ 2L G12C+ NSCLC**

<table>
<thead>
<tr>
<th>KRAS\textsuperscript{G12C} drug</th>
<th>RR</th>
<th>DOR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotorasib (PhII)</td>
<td>37%</td>
<td>10.0 m</td>
<td>6.8 m</td>
</tr>
<tr>
<td>Adagrasib (PhI/II)</td>
<td>45%</td>
<td>tbd</td>
<td>tbd</td>
</tr>
</tbody>
</table>

Hong et al., NEJM 2020, Jänne et al., ENA 2020; Li et al., WCLC 2020
Two future classes of KRAS medicines

SELECTIVE:
- G12D (26.4%)
- G12C (13.6%)

PAN:
- G12D (26.4%)
- G12V (21.3%)
- G12C (13.6%)
- G12A (4.4%)
- G13D (6.8%)
- Q51H (3.2%)
- G12R (4.5%)
Progress in Pan-KRAS approaches

- SOS1 Inhibitors: BI-3406, BI 1701963
- MEK1/2 Inhibitors: BI 3011441
- pan-KRAS Inhibitors: BI-panKRAS3
- pan-KRAS Degraders: BI-KRASdegrader1
- pan-RAS Inhibitors: BI-2852
How to expand the druggable cancer target space?

Boehringer Ingelheim collaboration with Forma Therapeutics:

- Start of collaboration in 2012
- Targeting key protein/protein interactions of major cancer drivers
- Screening both BI and Forma libraries
- Basis for SOS1::KRAS inhibitor program
Targeting Son of Sevenless: The pacemaker of KRAS

• SOS1 as key guanine nucleotide exchange factor (GEF) and pacemaker for KRAS “beating” = KRAS activation

• Majority of KRAS oncoproteins (e.g. KRAS G12C) remain dependent on nucleotide exchange for activation in cancer cells

• Treatment with RAF, MEK or ERK inhibitors leads to compensatory increase in SOS1 activity and GTP loading of RAS = KRAS re-activation

Broad therapeutic range of SOS1::KRAS inhibitors in KRAS-driven cancers?

Kessler, Gerlach, Kraut and McConnell, Curr Opin Chem Biol, 2021
BI-3406: Active against all major KRAS mutants

Antiproliferative effect in isogenic cell panel (3D):

G12 and G13 KRAS mutants susceptible to SOS1 inhibition

Exceptions:
• \( \text{KRAS}^{G12R} \): defective in SOS1 binding (Hobbs, 2020)
• \( \text{KRAS}^{Q61H} \): lack of intrinsic GTPase activity (Hunter, 2015)

Broad KRAS mutation coverage by SOS1::KRAS inhibitors
KRAS mutation status defines sensitivity to BI-3406

Sensitivity of 40 cancer cell lines treated with BI-3406 in 3D proliferation assays

- **Response to BI-3406**
  - Red: Resistant
  - Blue: Sensitive

- **Tumor type**
  - Breast carcinoma
  - Colon carcinoma
  - Melanoma
  - NSCLC
  - Ovarian carcinoma
  - Pancreas carcinoma
  - SCLC
  - Uterus carcinoma

- **Zygosity/WT**
  - 1.00
  - 0.75
  - 0.50
  - 0.25
  - 0.00

Hofmann et al., Cancer Discovery 2021
Vertical targeting of SOS1 plus MEK1/2

MIA PaCa-2 CDX (PDAC; KRAS<sup>G12C</sup>)

Vehicle Control
BI 1701963, 50mg/kg, bid
Trametinib, 0.1mg/kg, bid
Combination

PD Biomarker Modulation
Day 8 (mRNAs)

Combination MEK1/2 plus SOS1 inhibition

Adapted from Zhao, Xue and Lito, Cancer Discovery 2021

Presentation CT210 - Trial in Progress: Phase 1 studies of BI 1701963, a SOS1::KRAS inhibitor, in combination with MEK inhibitors, irreversible KRASG12C inhibitors or irinotecan #AACR21 by Hofmann et al.
KRAS fragment screening and structure-based drug design

1st & 2nd Site\textsuperscript{1} KRAS Fragment Screens

Structure-based Drug Design

Soaking systems\textsuperscript{3}

KRAS Drug Discovery Programs

Co-crystallization systems\textsuperscript{2}

- KRAS\textsuperscript{G12C} Inhibitors
- KRAS\textsuperscript{G12D} Inhibitors
- pan-KRAS Inhibitors
- pan-KRAS PROTACs
- pan-RAS Inhibitors\textsuperscript{2-4}

1. Sun \textit{et al}., J Biomol NMR 2014
2. Kessler \textit{et al}., PNAS 2019
3. Bergner \textit{et al}., Chemistry 2019

Stephen Fesik
BI-panKRAS1 is isotype selective for KRAS

Pan-KRAS PPI Inhibition
(BI-panKRAS1, GDP-RAS::SOS1 AlphaScreen)

Pan-RAS PPI Inhibition
(BI-2852¹, GDP-RAS::SOS1 AlphaScreen)

IC₅₀ GDP-KRASG12D::SOS1 19 nM 824 nM
IC₅₀ GDP-KRASwt::SOS1 91 nM 459 nM
IC₅₀ GDP-HRASwt::SOS1 ~20,000 nM 915 nM
IC₅₀ GDP-NRASwt::SOS1 ~20,000 nM 635 nM

¹ Kessler et al., PNAS 2019

Indirect target engagement marker
(pERK-Mesoscale assay, day 5)

Disease modulation marker
(Ki67 IHC, day 5)

BI-panKRAS3

Significant reduction of pERK (~75%) and reduction of Ki67+ cells (~95%)

**, p<0.01, ctrl vs. treated one-way ANOVA
BI-panKRAS3: Anti-tumor activity in CRC *in-vivo* models

**GP2d CDX (KRAS$^{G12D}$)**

<table>
<thead>
<tr>
<th>Dose [mg/kg]</th>
<th>Schedule</th>
<th>TGI [d50]</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>qd bid</td>
<td>80</td>
</tr>
<tr>
<td>90</td>
<td>qd bid</td>
<td>113</td>
</tr>
</tbody>
</table>

**HCT15 CDX (KRAS$^{G13D}$)**

<table>
<thead>
<tr>
<th>Dose [mg/kg]</th>
<th>Schedule</th>
<th>TGI [d50]</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>qd bid</td>
<td>31</td>
</tr>
<tr>
<td>90</td>
<td>qd bid</td>
<td>97</td>
</tr>
</tbody>
</table>

**Tumor Volume [mm$^3$]**

**Median Weight Change [%]**

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Feedback blockade through SOS1 inhibitor combination

Adapted from Zhao, Xue and Lito, Cancer Discovery 2021

KRASi = BI-panKRAS4 (2 μM)
SOS1i = BI-3406 (500 nM)
Proteolysis targeting chimeras (PROTACs)

PROTACs highjack a ligase to degrade disease causing proteins

Farnaby, Koegl, McConnell and Ciulli, Curr Opin Pharmacol, 2021
KRAS PROTAC ternary complex

GDP-KRAS\textsuperscript{G12D}::SOS1 FRET assay

- \( K_D \) ternary (+E3)
- \( K_D \) binary (-E3)

Response [%] vs. BI-KRASdegrader1 concentration [nM]

> 10 fold

W. Farnaby, A. Ciulli, D. Zollman

J. Popow, A. Gollner, T. Gerstberger

2021 AACR Annual Meeting, May 17-21, 2021, Norbert Kraut
BI-KRASdegrader1: Activity in KRAS-dependent cell lines

**Mutant KRAS Degradation**
- GP5d (G12D): 2 nM
- SK-CO-1 (G12V): 55 nM

**pERK Inhibition**
- 16 h
- 2 h

**Proliferation**
- Inactive Control
- KRAS PROTAC
- 27 nM
- 116 nM

2021 AACR Annual Meeting, May 17-21, 2021, Norbert Kraut
KRAS status defines sensitivity to BI-KRASdegrader1

**KRAS PROTAC degradation of KRAS mutants**
(GP5d cell-line transduced with HiBit (Promega)-tagged KRAS)

<table>
<thead>
<tr>
<th>Mutant</th>
<th>D&lt;sub&gt;max&lt;/sub&gt; [%]</th>
<th>DC&lt;sub&gt;50&lt;/sub&gt; [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>G12D</td>
<td>96</td>
<td>1</td>
</tr>
<tr>
<td>G12V</td>
<td>91</td>
<td>4</td>
</tr>
<tr>
<td>G12C</td>
<td>93</td>
<td>2</td>
</tr>
<tr>
<td>G12D</td>
<td>94</td>
<td>3</td>
</tr>
<tr>
<td>G12C</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>G12D</td>
<td>96</td>
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<td>G12V</td>
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<td>G12D</td>
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<td>G12V</td>
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<td>G12C</td>
<td>73</td>
<td>&gt;9k</td>
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<tr>
<td>G12D</td>
<td>94</td>
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<td>G12V</td>
<td>90</td>
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<tr>
<td>G12C</td>
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<td>1</td>
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<td>G12D</td>
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<tr>
<td>G12V</td>
<td>86</td>
<td>1</td>
</tr>
<tr>
<td>G12C</td>
<td>96</td>
<td>1</td>
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</tbody>
</table>

All mutants except strongly GTP hydrolysis-impaired KRAS mutants degraded
KRAS status defines sensitivity to BI-KRASdegrader2

KRAS status:  
- Mutant / Wild type amplified  
- Wild type

IC50 [µM]  
- 0.01  
- 0.1  
- 1  
- 10

320 Cancer cell line panel

KRAS mutation/amplification status as biomarker of BI-KRASdegrader2 sensitivity
Progress in mutant-selective KRAS programs

- **G12D (26.4%)**
- **G12C (13.6%)**

**SELECTIVE**

**KRAS\textsuperscript{G12C} Inhibitors**: BI 1823911

**KRAS\textsuperscript{G12D} Inhibitors**: BI-KRASG12D1
BI 1823911 is a potent and selective KRAS\textsuperscript{G12C} inhibitor

3-fold improved anti-proliferative activity compared to AMG 510 and MRTX849

1271 – In vitro and in vivo characterization of BI 1823911 – a novel KRAS\textsuperscript{G12C} selective small molecule inhibitor – #AACR21 by Savarese et al.

H. Lu, A. Machado, J. Daniele, C. Vellano, T. Heffernan, J. Marszalek

J. Phan, A. Waterson, S. Fesik


2021 AACR Annual Meeting, May 17-21, 2021, Norbert Kraut
**In vivo efficacy of BI 1823911 in NSCLC and CRC models**

Antitumor activity of BI 1823911 in KRAS$^{G12C}$-mutant CDX and PDX human tumor xenograft models

Comparison to AMG 510 and MRTX849

Efficacy of 60 mg/kg BI 1823911 is comparable to 100 mg/kg AMG 510 or MRTX849
Therapeutic opportunity: Targeting KRAS\textsuperscript{G12C} plus SOS1

Combination KRAS\textsuperscript{G12C} plus SOS1 inhibition
- SOS1 inhibitors shift equilibrium from active KRAS (ON) towards the inactive KRAS (OFF) form
- SOS1 inhibitors enhance the effect of inactive state-selective KRAS\textsuperscript{G12C} inhibitors

\textit{In vitro} pathway modulation by BI 1823911 and BI 1701963

<table>
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<tr>
<th>NCI-H2122</th>
<th>6h</th>
<th>24h</th>
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<tr>
<td>DMSO</td>
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</table>

Zhao, Xue and Lito, Cancer Discovery 2021
Therapeutic opportunity: Targeting $\text{KRAS}^{G12C}$ plus SOS1

- SOS1::pan-KRAS inhibitors sensitize KRAS G12C mutant tumors to covalent KRAS G12C inhibitors that bind to KRAS(OFF).

- Phase 1 clinical studies of BI 1823911 in monotherapy and in combination with SOS1i expected to begin in 2021. Phase 1 studies of MRTX849 in combination with SOS1i will start in 2021.
Targeting KRAS<sup>G12D</sup> mutations

**pERK Pathway Inhibition**
(NCI-H23 isogenic cell-lines, Surefire, 1 hour)

<table>
<thead>
<tr>
<th>H23 Clone</th>
<th>BI-panKRAS5</th>
<th>BI-KRASG12D1</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>71 nM</td>
<td>1,500 nM</td>
</tr>
<tr>
<td>G12C</td>
<td>89 nM</td>
<td>4,800 nM</td>
</tr>
<tr>
<td>G12D</td>
<td>53 nM</td>
<td>36 nM</td>
</tr>
<tr>
<td>G12V</td>
<td>160 nM</td>
<td>6,300 nM</td>
</tr>
<tr>
<td>G12R</td>
<td>5,000 nM</td>
<td>10,000 nM</td>
</tr>
<tr>
<td>Q61H</td>
<td>64 nM</td>
<td>1,200 nM</td>
</tr>
</tbody>
</table>

**Apoptosis: cleaved caspase 3**
(NCI-H23 Isogenic cell-lines)

M. Gmachl, T. Markovic, T. Wunberg, C. Smethurst
B. Wilding, J. Broecker, L. Herdeis, D. Gerlach

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Two future classes of KRAS medicines

**KRAS CLUSTER APPROACH**

**1. Mutant-selective KRAS Drugs**
- **KRAS G12C**
- **KRAS G12D**

**Opportunities**
- Deep and durable target inhibition
- Low risk of KRAS WT-mediated toxicity
- Choice for early line settings

**Open issues**
- More prone to acquired resistance?
- NCE feasibility beyond G12C and G12D

**Pan KRAS Drugs**
- Pan-KRAS inhibitors
- Pan-KRAS degraders

**Opportunities**
- Addresses broad patient population
- Early line settings lacking allele-specific inhibitors
- Cancers driven by KRAS WT (e.g. KRAS\textsuperscript{AMP})
- Heterogenous cancers driven by multiple KRAS aberrations

**Open issues**
- KRAS WT-mediated toxicity
- Capability to address resistance to allele-specific inhibitors\textsuperscript{1}

---

\textsuperscript{1} KRAS G12C inhibitor resistance: Tanaka et al., Cancer Discov 2021; Awad et al., AACR Annual Meeting 2021
Conclusions and outlook

- Targeting KRAS will extend the benefits of genome-driven oncology
- Clinical breakthroughs for allele-specific KRAS G12C inhibitors, multiple rational combinations underway
- Progress in drugging other KRAS mutants with allele-specific inhibitors, eg KRAS G12D – Feasibility for other KRAS mutants t.b.d.
- Strong rationale for pan-KRAS concepts, including SOS1 plus MEK1/2 combinations, direct pan-KRAS inhibitors and pan-KRAS degraders
- SOS1 in regulating feedback reactivation across the KRAS inhibitor space
- Drugging of all the major KRAS mutant variants and advancing rational combinations for all KRAS-driven cancers as key goal for the next years
Thanks to the entire BI team & collaborators

https://bi-placetobe.com/

https://opnme.com/

InOncology.com
Boehringer Ingelheim