Discovery of GDC-6036, a clinical stage treatment for *KRAS* G12C-positive cancers

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Disclosure Information

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I have the following relevant financial relationships to disclose:

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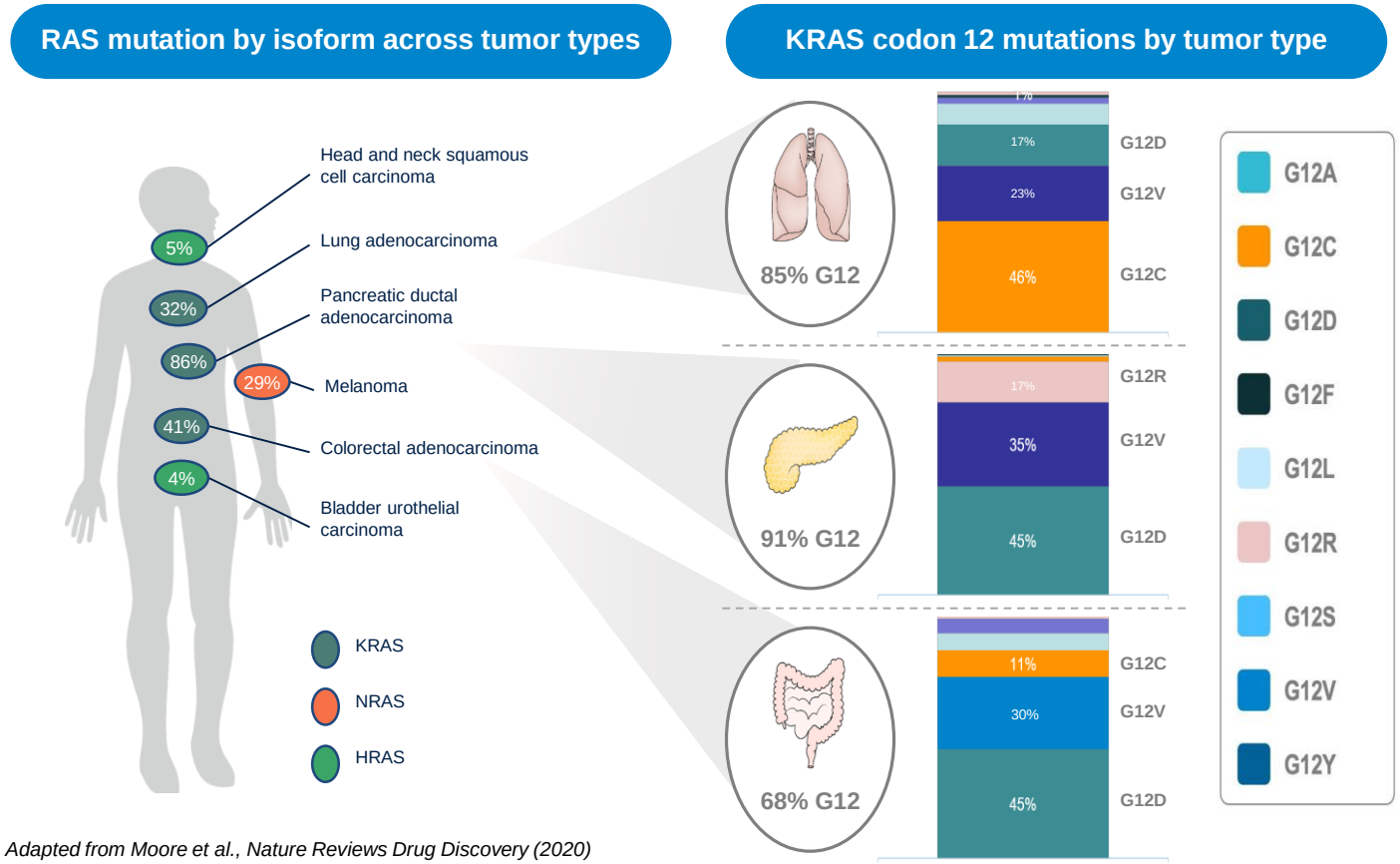
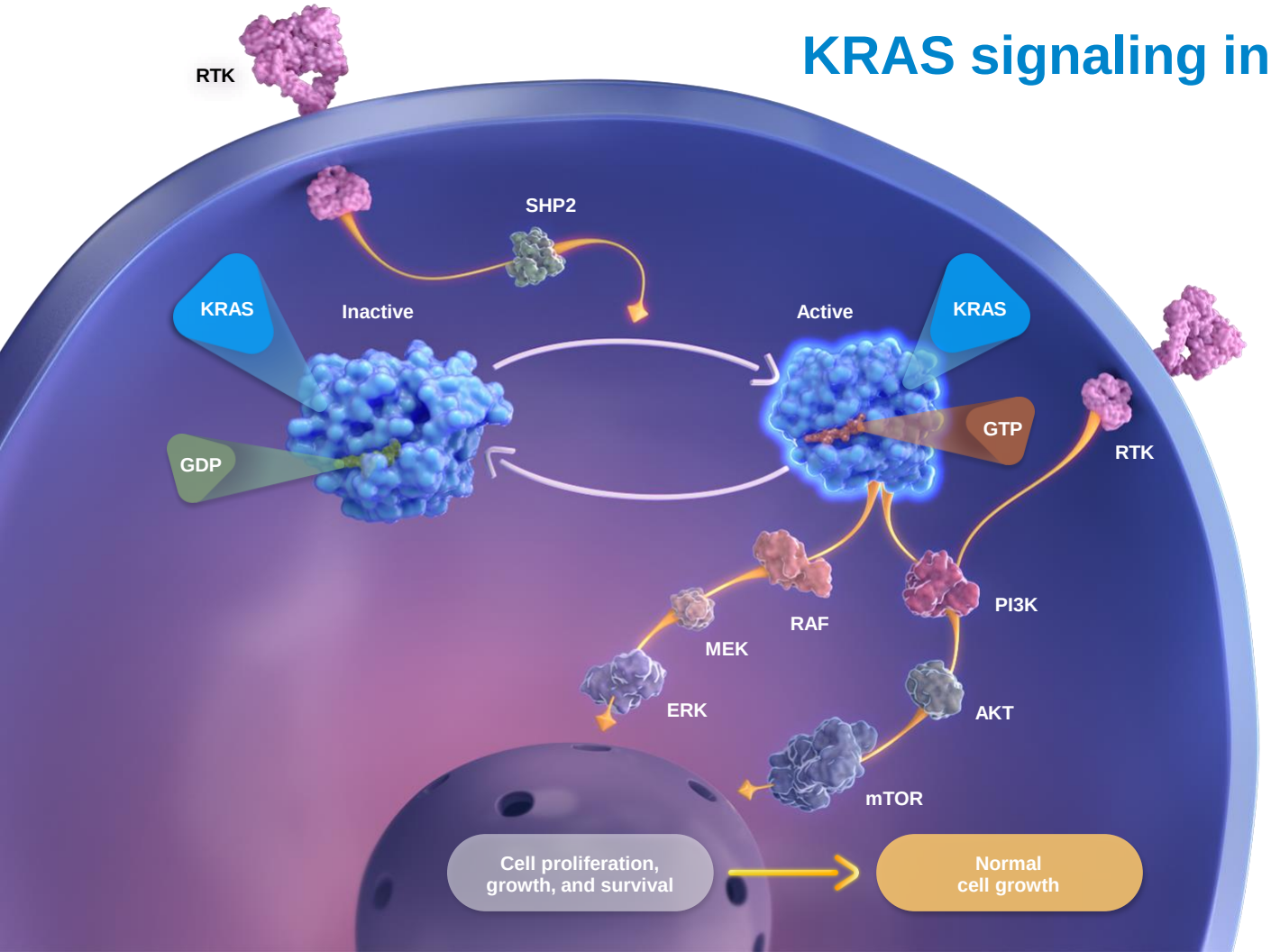
Mutations in *KRAS* are the most common oncogenic driver mutations found in human cancer



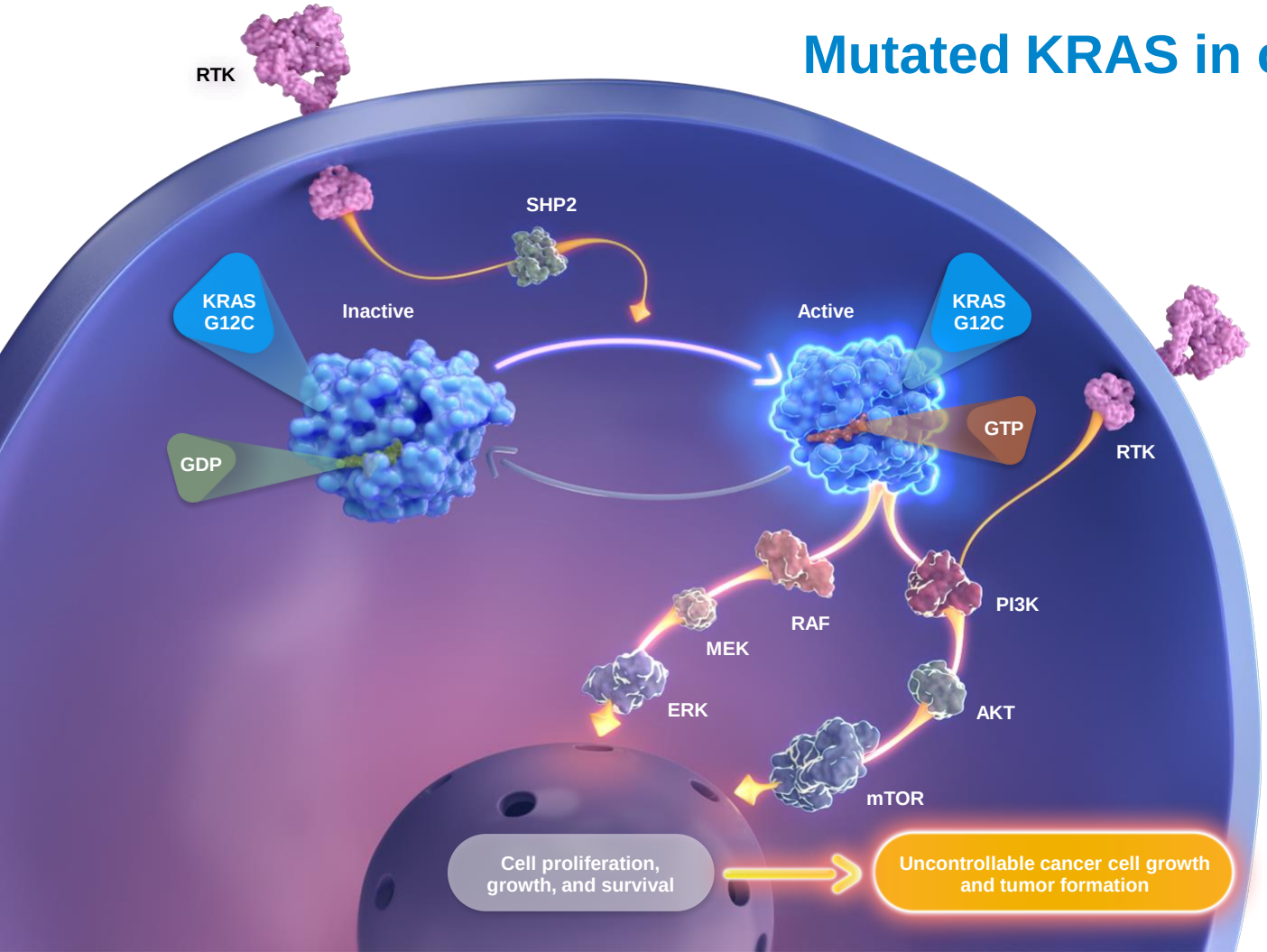
Adapted from Moore et al., Nature Reviews Drug Discovery (2020)

KRAS signaling in normal cells



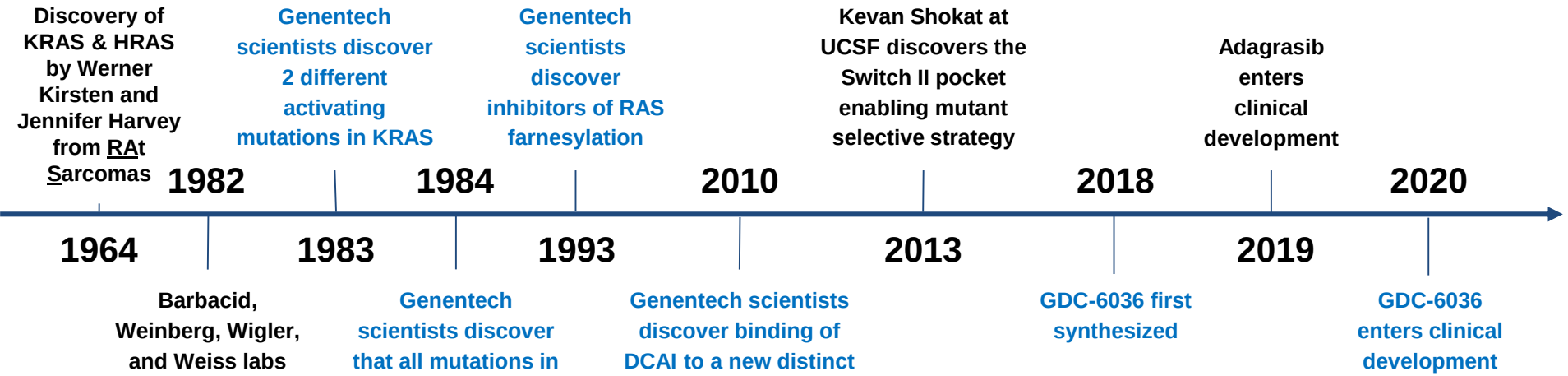
- KRAS is a signaling GTPase that cycles between active GTP-bound and inactive GDP-bound states to regulate intracellular signaling in response to extracellular growth factors
- GTP-bound KRAS activates multiple downstream signaling pathways involved in cell proliferation, migration, and survival

Mutated KRAS in cancer



- Oncogenic mutations in KRAS, such as G12C, interfere with the transition from GTP-bound to GDP-bound states
- Locking KRAS G12C in its constantly active state increases downstream oncogenic signaling, resulting in uncontrollable cancer cell growth and tumor formation

Genentech has a long history in the biology and targeting of RAS

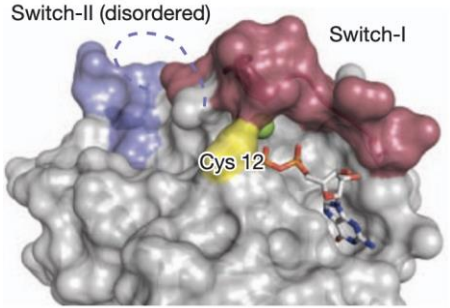


Timeline not to scale

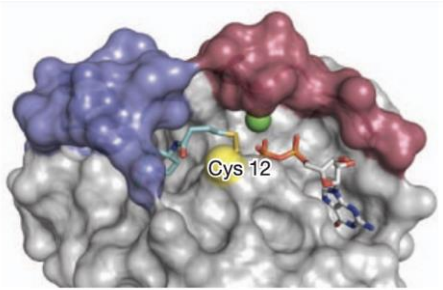
Landmark discovery for selective targeting of KRAS G12C

K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions

Jonathan M. Ostrem[1]*, Ulf Peters[1]*, Martin L. Sos[1], James A. Wells[2] & Kevan M. Shokat[1]



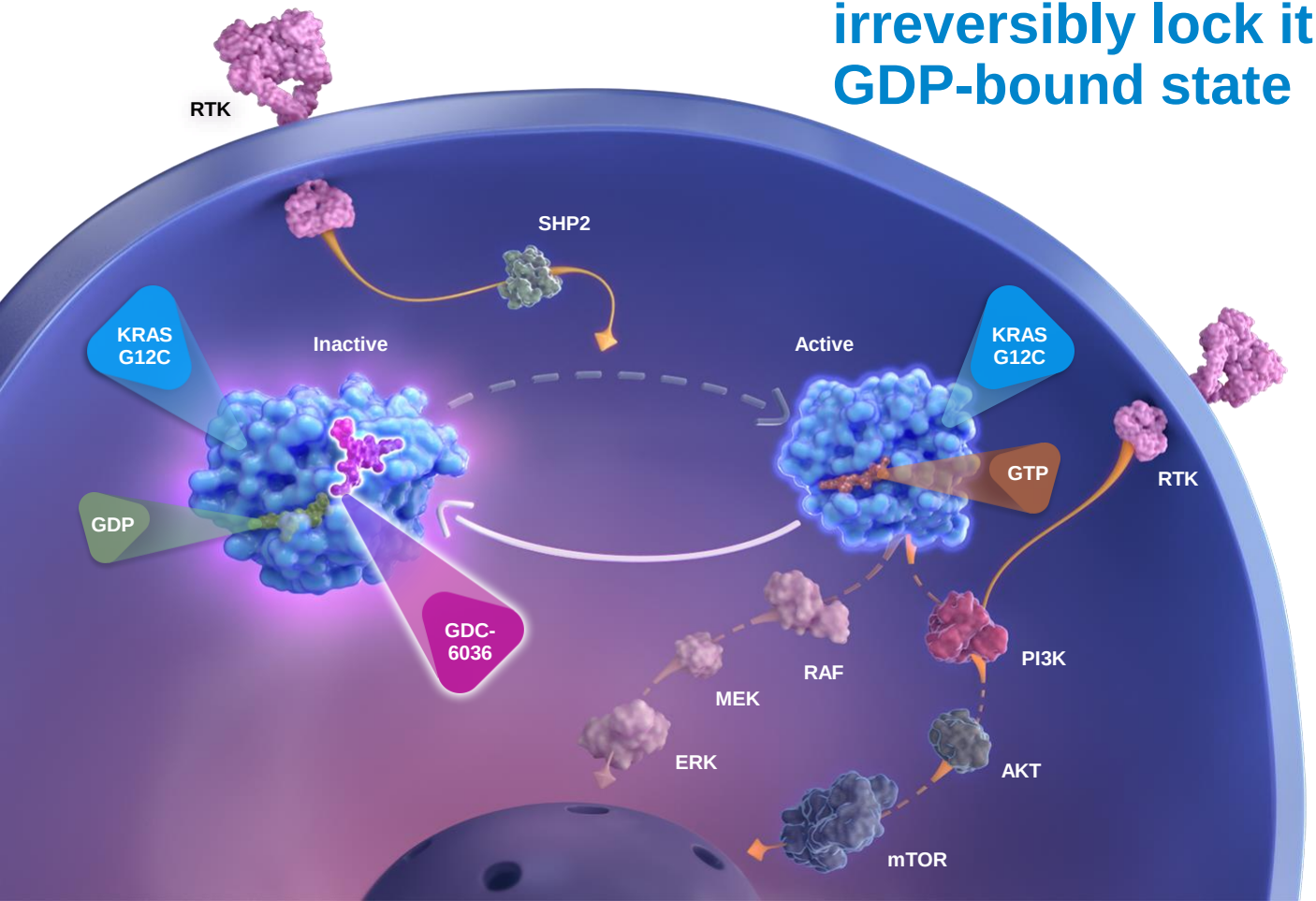
GDP-bound KRAS G12C structure, showing disordered Switch-II domain



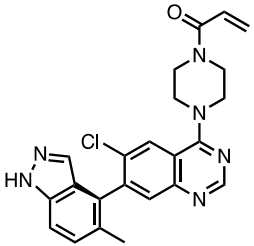
Disulfide-tethering screen identified fragments that targeted Cys12 identifying a novel pocket near Switch-II domain

Ostrem JM, et al. 2013. Nature; 503: 543-551.

Covalent inhibitors of KRAS G12C irreversibly lock it in the inactive GDP-bound state



New functionality improves KRAS G12C potency

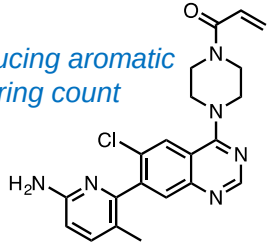


1*

HTRF IC_{50} = 190 nM

Cell alk. EC_{50} = 1000 nM

Reducing aromatic ring count

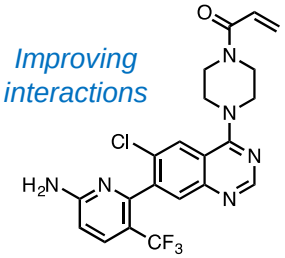


2

HTRF IC_{50} = 450 nM

Cell alk. EC_{50} = 2800 nM

Improving interactions

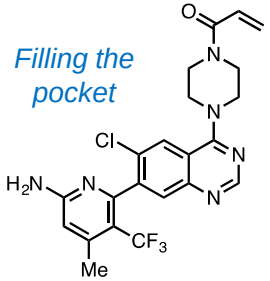


3

HTRF IC_{50} = 63 nM

Cell alk. EC_{50} = 450 nM

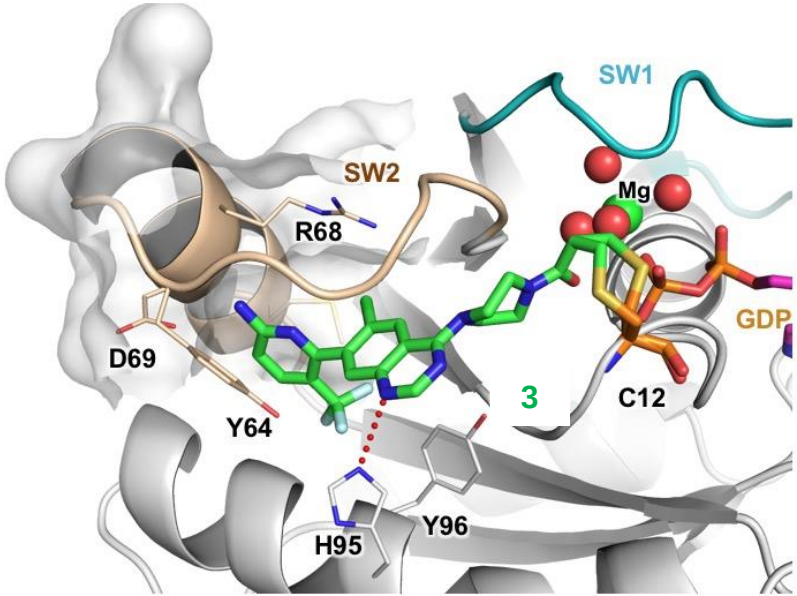
Filling the pocket



4

HTRF IC_{50} = 1.9 nM

Cell alk. EC_{50} = 79 nM

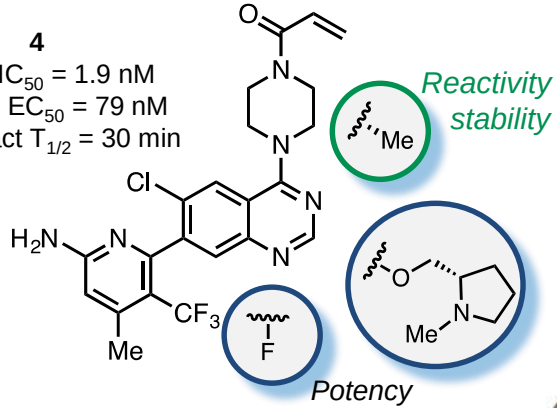


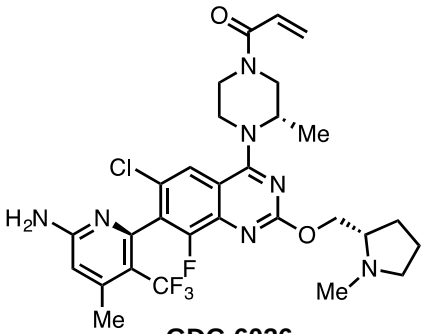
*WO2015054572

All assay data: 18h incubation with inhibitor

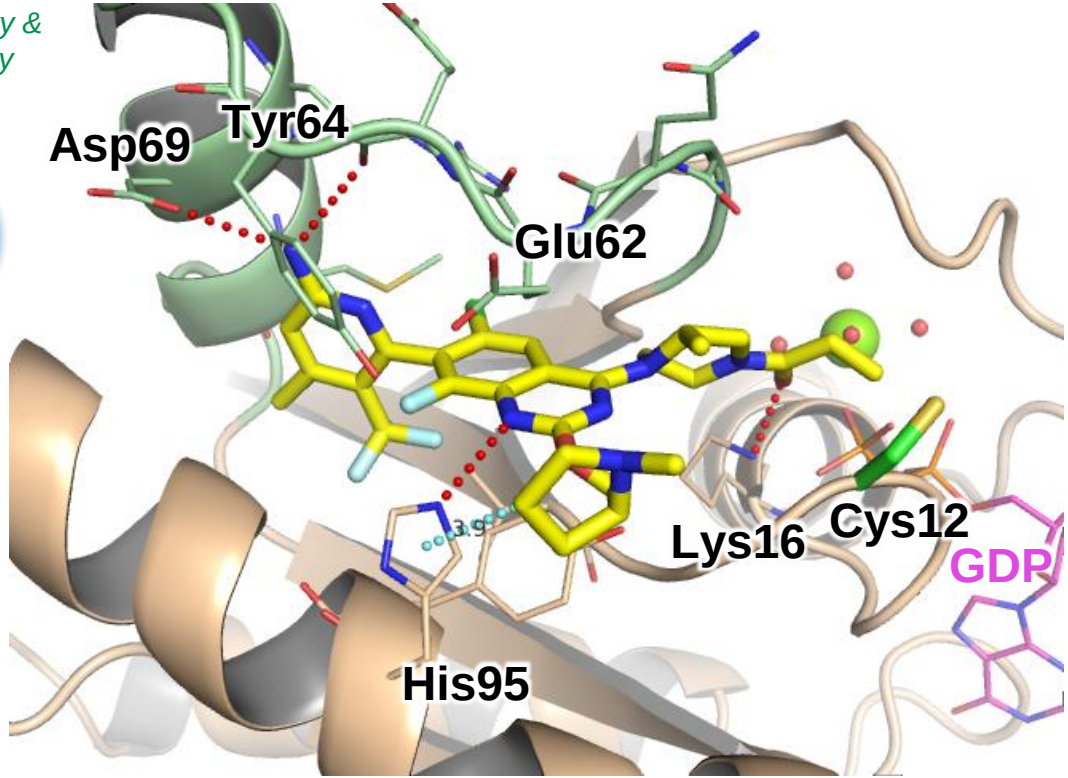
Discovery of GDC-6036

4
HTRF IC_{50} = 1.9 nM
Cell alk. EC_{50} = 79 nM
Cys. React $T_{1/2}$ = 30 min





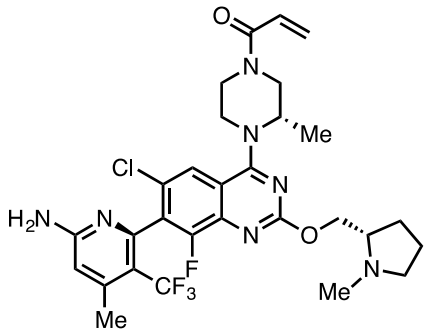
GDC-6036
HTRF IC_{50} 0.0029 nM
Cell alk. EC_{50} = 0.52 nM
Cys. React $T_{1/2}$ = 55 min



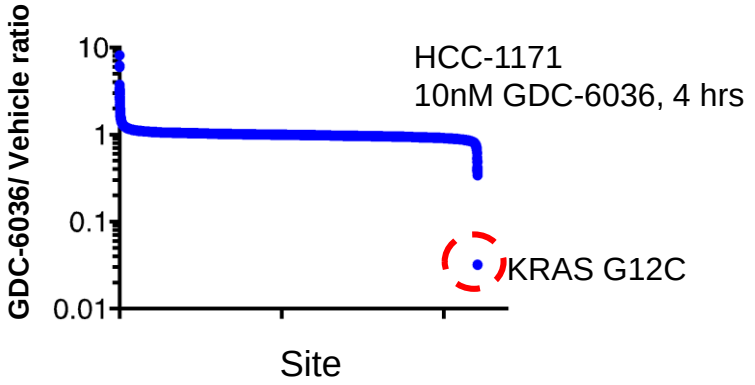
X-ray co-crystal structure of KRAS G12C:GDC-6036

GDC-6036 is an exceptionally potent and selective covalent KRAS G12C inhibitor

	GDC-6036
MW, TPSA, logD	622, 100, 2.3
Kinetic Solubility	130 μM
G12C HTRF IC_{50}	0.0029 nM
G12C K_{inact}/K_i	710,000 $(M*s)^{-1}$
HCC1171 Alkylation EC_{50}	0.32 nM
H358 K_{inact}/K_i	27,000 $(M*s)^{-1}$
Median Cell Potency / Sel.	0.18 nM /16,000X
LM H/R/M/D/C [mL/min/kg]	10 / 15 / 53 / 13 / 35
Hep H/R/M/D/C [mL/min/kg]	12 / 13 / 46 / 21 / 30
PPB H/R/M/D/C [%}	99.8 / 95.9 / 98.2 / 93.5 / 99.8
gMDCK AB / MDRI Ratio	5 / 280
WBS $T_{1/2}$ H/R/M/D/C [min]	310 / 170 / 360 / 80 / 140
Cys Reactivity $T_{1/2}$	55 min
Mouse CL, $T_{1/2}$, V_{ss}, F	24 mL/min/kg, 1.4 hr, 2.0 L/kg, 17%
Rat CL, $T_{1/2}$, V_{ss}, F	69 mL/min/kg, 1.4 hr, 5.4 L/kg, 6%
Dog CL, $T_{1/2}$, V_{ss}, F	75 mL/min/kg, 1.2 hr, 4.5 L/kg, 25%
Cyno CL, $T_{1/2}$, V_{ss}, F	10 mL/min/kg, 1.4 hr, 1.2 L/kg, 5%

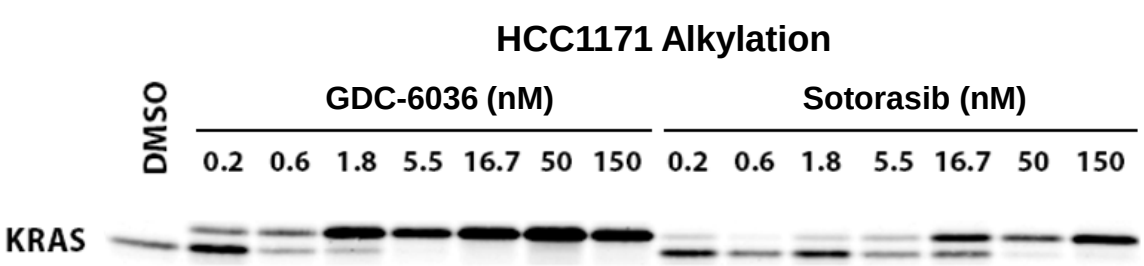


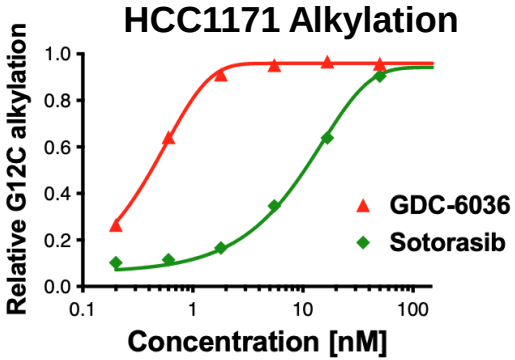
Selective in Proteomics (~5000 proteins):

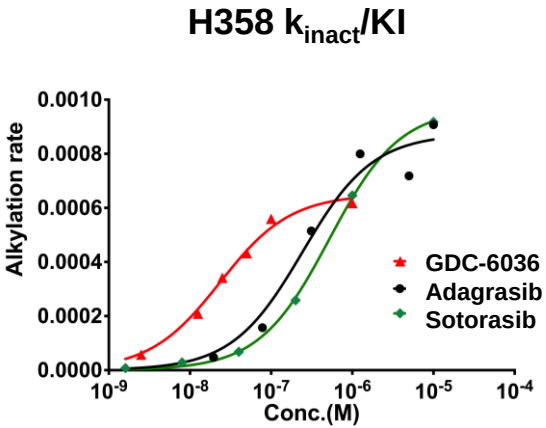


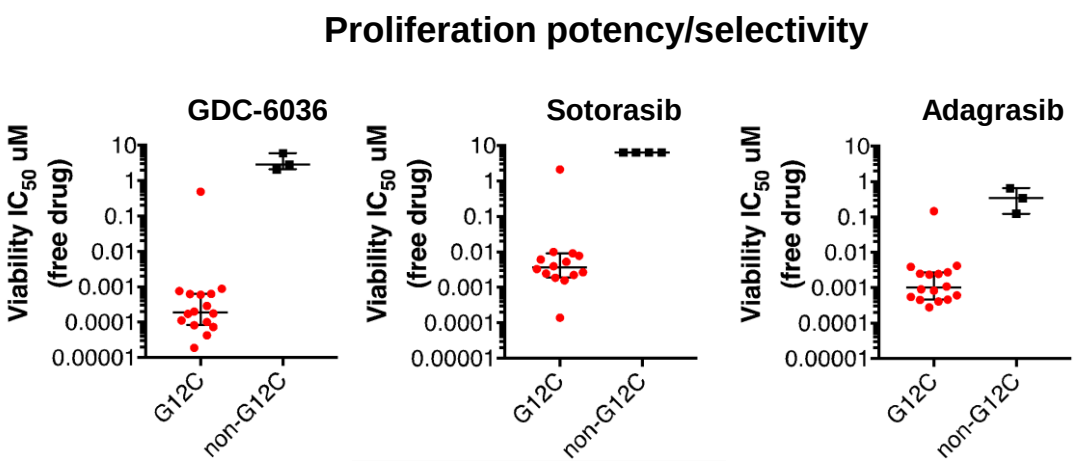
LM: Liver Microsomes; Hep: Hepatocytes; PPB: Plasma Protein Binding; WBS: Whole Blood Stability

GDC-6036 is more potent and selective *in vitro* than other clinical KRAS G12C inhibitors









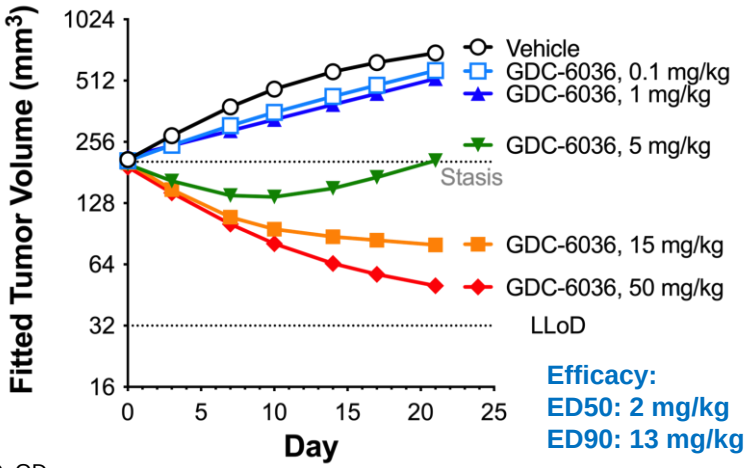
GDC-6036 is more potent and selective *in vitro* than other clinical KRAS G12C inhibitors

	KRAS G12C HTRF IC_{50} (nM)	KRAS G12C k_{inact}/K_I $(M*s)^{-1}$	NCI-HCC1171 Alkylation IC_{50} (nM)	NCI-H358 k_{inact}/K_I $(M*s)^{-1}$	Median Cell Prolif IC_{50} (nM) / Selectivity
GDC-6036	0.0029	710,000	0.32	27,000	0.18 / 16,000 X
Sotorasib	1.4	7900	7.9	1900	3.4 / >1800 X
Adagrasib	0.058	89,000	8.7‡	1500	1.0 / 340 X
GDC-6036 Comparison	20-480 X	8-90 X	25-27 X	14-18 X	6-19 X / <9-47 X

‡ Alternate assay format due to technical limitations

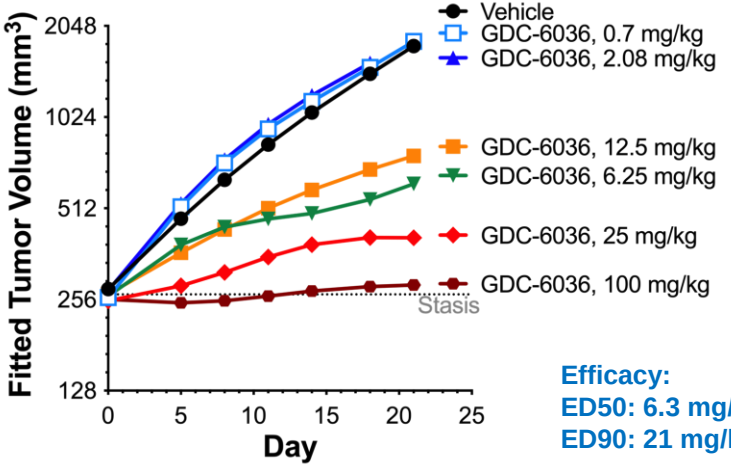
Anti-tumor efficacy of GDC-6036 in KRAS G12C-positive NSCLC tumor models

NCI-H358 (higher sensitivity)
Regressions as low as 5 mg/kg QD



Efficacy:
ED50: 2 mg/kg
ED90: 13 mg/kg

NCI-H2122 (lower sensitivity)
Stasis achieved at 100 mg/kg



Efficacy:
ED50: 6.3 mg/kg
ED90: 21 mg/kg

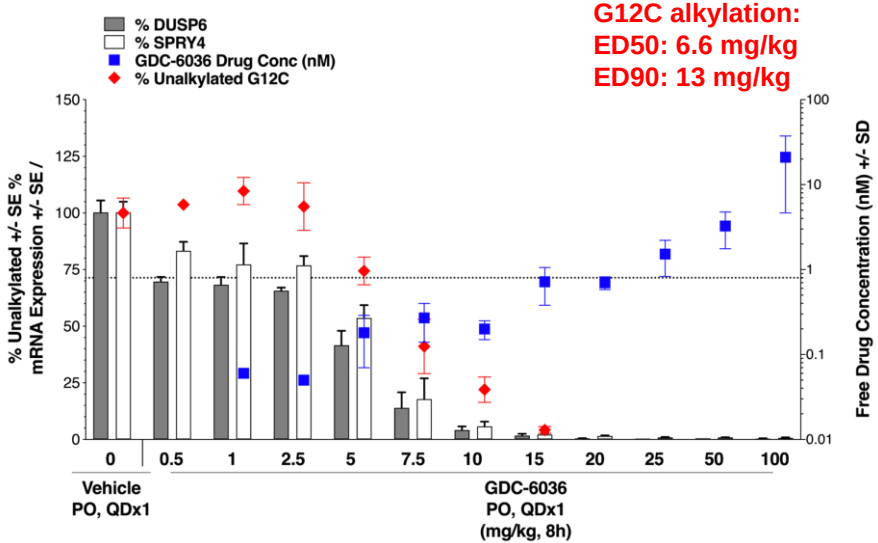
All dosing, PO, QD
All treatments well-tolerated

- Maximal response achieved in vivo varies by innate sensitivity of the cell line
- ED50/90 values for achievable efficacy modestly higher in NCI-H2122, but not dramatically different (1.5-3x higher)

PK/PD alkylation is consistent with xenograft efficacy

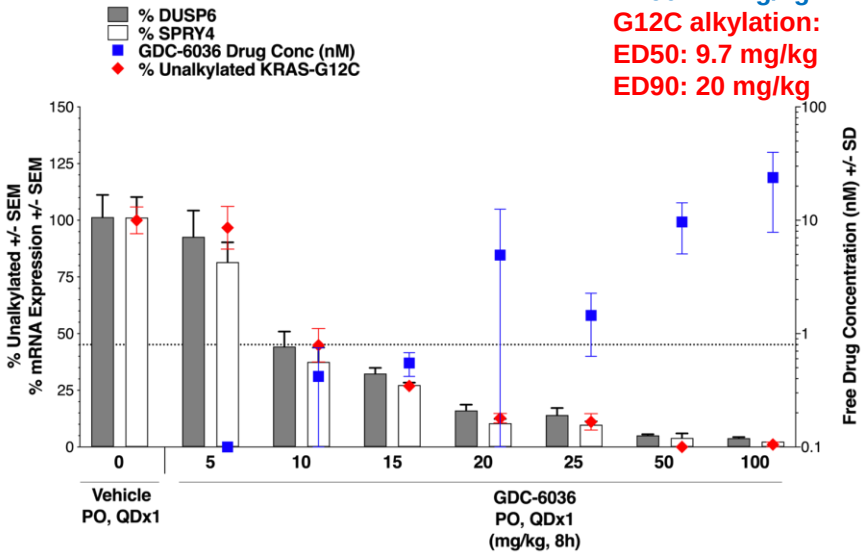
NCI-H358

Efficacy:
ED50: 2 mg/kg
ED90: 13 mg/kg
G12C alkylation:
ED50: 6.6 mg/kg
ED90: 13 mg/kg



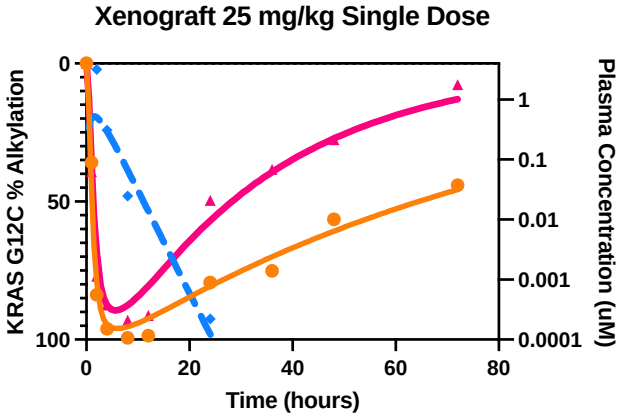
NCI-H2122

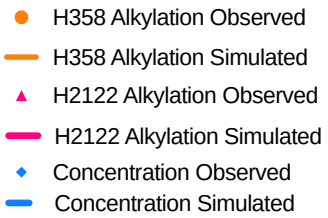
Efficacy:
ED50: 6.3 mg/kg
ED90: 21 mg/kg
G12C alkylation:
ED50: 9.7 mg/kg
ED90: 20 mg/kg



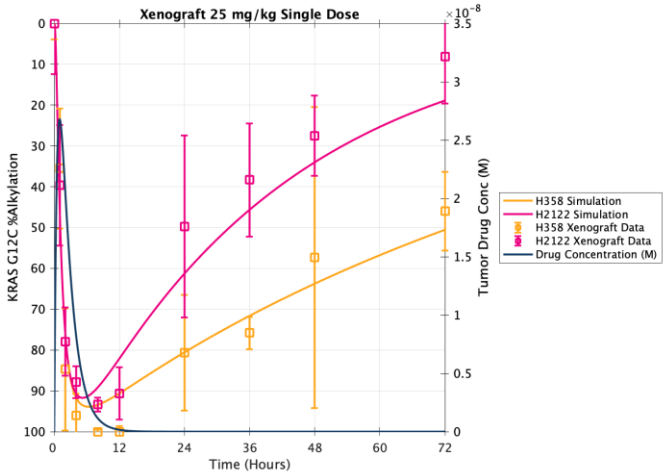
- KRAS G12C alkylation/MAPK target gene modulation (*DUSP6*/*SPRY4*) are highly correlated
- ED50/90 values ~1.5-2x higher in NCI-H2122, in line with efficacy ED50/90 values

Preclinical PK/PD modeling of KRAS G12C mutant tumor models help guide clinical dose projections





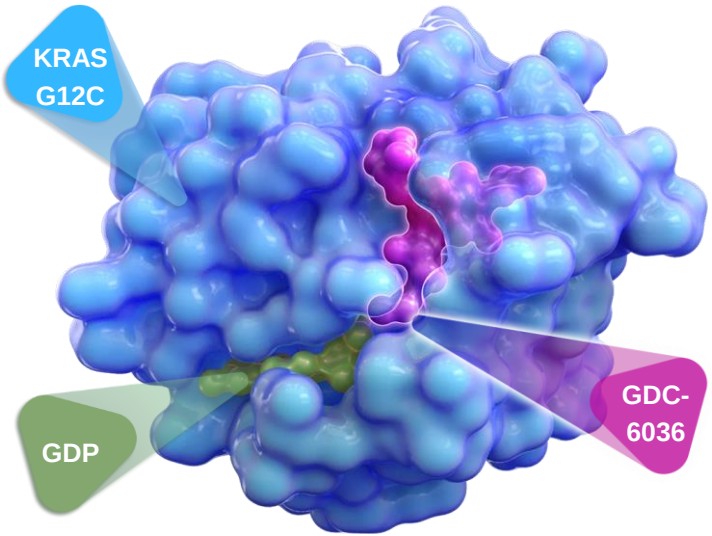
Mechanistic Model



QSP Model

- Preclinical data were employed to build a mechanistic PK/PD model as well as a Quantitative Systems Pharmacology (QSP) model to predict the human dose.
- Preclinical human dose projections estimated a dose <400 mg will cover 90% alkylation / IC_{90} in H2122 at C_{trough}

Summary



GDC-6036:

- Irreversibly alkylates KRAS G12C and locks it in the inactive GDP-bound state
- Is more potent and more selective *in vitro* than sotorasib and adagrasib
- Exhibits significant anti-tumor efficacy across *KRAS* G12C-positive models
- Currently is in Phase 1 clinical development (NCT04449874) as monotherapy and in multiple combinations with other agents, including SHP2 inhibitor GDC-1971*

**Bret Williams, et al. Discovery and characterization of the potent, allosteric SHP2 inhibitor GDC-1971 for the treatment of RTK/RAS driven tumors [Abstract #3327/5; posted April 12, 2022]*