IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Phase Ia study to evaluate GDC-6036 monotherapy in patients with non-small cell lung cancer (NSCLC) with *KRAS G12C* mutation

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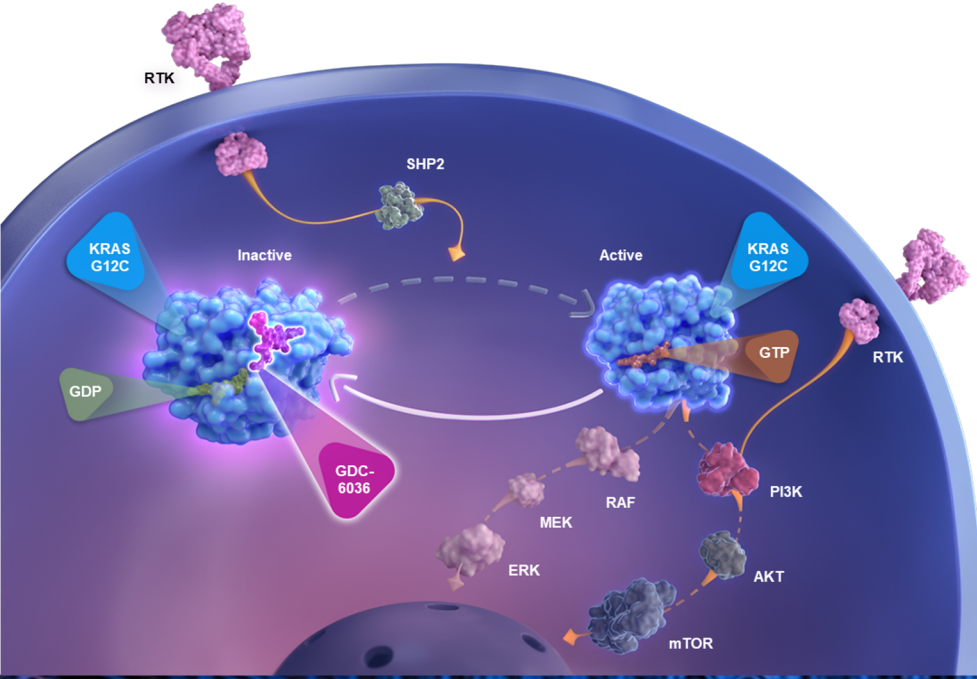
DISCLOSURES

Commercial Interest	Relationship(s)
Genentech, Inc.	Honoraria/consulting, Research funding
AstraZeneca	Honoraria/consulting, Research funding
Amgen	Honoraria/consulting

GDC-6036 is a potent, selective, covalent inhibitor of KRAS G12C



- *KRAS G12C* is one of the most common oncogenic mutations in NSCLC
- GDC-6036 is an oral, highly potent, and selective KRAS G12C inhibitor that irreversibly locks the protein in an inactive state to turn off its oncogenic signaling
- GDC-6036 has been shown to be more potent and selective *in vitro* than sotorasib and adagrasib[1]

[1]Purkey et al. AACR 2022.

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Phase I study evaluates single agent GDC-6036 in advanced or metastatic solid tumors with *KRAS G12C* mutation

KEY ELIGIBILITY CRITERIA

- Locally advanced or metastatic solid tumors, including NSCLC, harboring a *KRAS G12C* mutation
- At least one prior treatment or intolerability of standard therapy
- Measurable or evaluable disease per RECIST
- Previously treated brain metastases only
- No prior KRAS G12C inhibitor treatment

DOSE ESCALATION

GDC-6036 oral QD, 21-day cycles

50mg → 100mg → 200mg → 400mg *Max Admin Dose*

N=6 N=5 N=10 N=6

NSCLC N=27

DOSE EXPANSION

GDC-6036 oral QD, 21-day cycles

400mg

NSCLC N=32

KEY ENDPOINTS

- Safety
- Pharmacokinetics
- Preliminary antitumor activity

GO42144, NCT04449874 - Data presented as of CCOD 13 May 2022: **N=135 patients across indications and N=59 NSCLC patients**

Disposition and baseline demographics: NSCLC

NSCLC patients enrolled	N=59
NSCLC patients enrolled at 400 mg	38 (64%)
NSCLC patients discontinued from study treatment	25 (42%)

Reasons for treatment discontinuation:

- Progressive disease 15 (25%)
- Adverse event 4 (7%)
- Physician decision 3 (5%)
- Clinical progression 2 (3%)
- Withdrawal by subject 1 (2%)

	NSCLC patients N=59
Age, median (range), years	67 (43 - 82)
Sex, female	33 (56%)
Smoking status, current or former	55 (93%)
ECOG 0 vs 1	21 (36%) vs 38 (64%)
PD-L1 positive (based on local test results), % (N=45)	56%
Median number of prior therapies in metastatic setting (N=58)	1 (0 - 5)
Prior checkpoint inhibitor	51 (86%)
Prior platinum chemotherapy	53 (90%)
Time on treatment, median (range), months	4.2 (0 - 18.1)

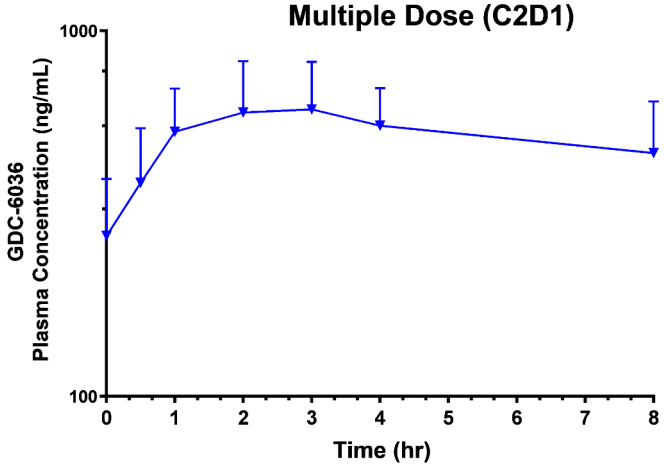
Summary of adverse events: NSCLC and all solid tumors

TREATMENT-RELATED AEs (≥10 PATIENTS) OVERALL & CORRESPONDING GRADE 3-5 AEs	NSCLC Patients N=59		All Patients N=135	
	Related AEs	Related Grade 3-5 AEs	Related AEs	Related Grade 3-5 AEs
Patients with at least one AE	52 (88.1%)	10 (16.9%)	119 (88.1%)	15 (11.1%)
Nausea	45 (76.3%)	0	94 (69.6%)	0
Diarrhea	36 (61%)	2 (3.4%)	82 (60.7%)	5 (3.7%)
Vomiting	32 (54.2%)	0	68 (50.4%)	0
Fatigue	14 (23.7%)	1 (1.7%)	26 (19.3%)	1 (0.7%)
Decreased appetite	9 (15.3%)	0	16 (11.9%)	0
Alanine aminotransferase increased	8 (13.6%)	4 (6.8%)	12 (8.9%)	4 (3%)
Aspartate aminotransferase increased	6 (10.2%)	3 (5.1%)	11 (8.1%)	3 (2.2%)
Dyspepsia	4 (6.8%)	0	10 (7.4%)	0

TREATMENT-RELATED AEs	NSCLC Patients N=59	All Patients N=135
Patients with AEs resulting in GDC-6036 modification (interruption/reduction/withdrawal)	21 (36%)	31 (23%)
Patients with AEs resulting in GDC-6036 reduction	11 (19%)	14 (10%)
Patients with AEs resulting GDC-6036 withdrawal	3 (5%)	3 (2%)

- Common treatment-related AEs: nausea, vomiting, and diarrhea
  - Most events Grade 1, occurred early in study treatment
- No dose-limiting toxicities reported
- Grade 5 events in 7 patients, all related to disease progression and none related to drug
- **Overall, AEs were manageable with supportive medications and dose modifications**

Pharmacokinetics: All solid tumors



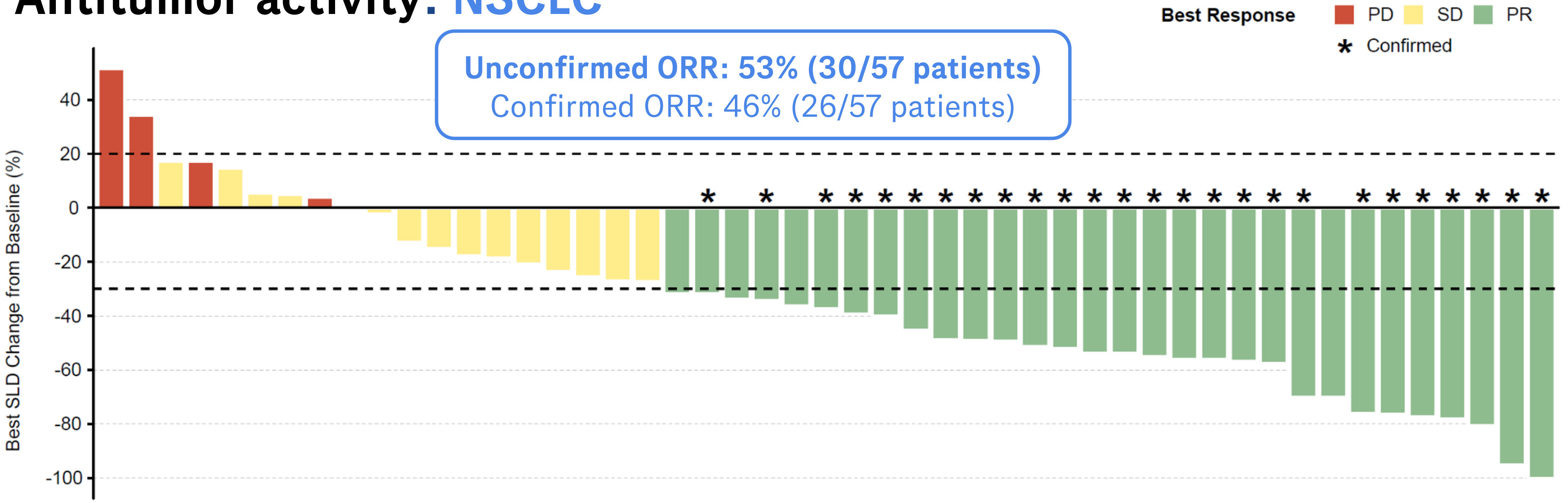
Steady State Pharmacokinetic Parameters of GDC-6036 (400 mg QD, N=34)

Dose (mg)	Study Day	t_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (hr · ng/mL)	Accumulation
400	C2D1	3.0 (0.5-8.0)	684 ± 213	9900 ± 3240	1.5 ± 0.4

- Following a single dose (50-400 mg) of GDC-6036, mean $t_{1/2}$ ranged from 13 to 17 hours, compatible with QD dosing
- Majority of patients treated at the expansion dose (400 mg QD) of GDC-6036 are predicted to achieve exposures corresponding to maximal covalent target engagement from nonclinical studies

Antitumor activity: NSCLC

Unconfirmed ORR: 53% (30/57 patients)
Confirmed ORR: 46% (26/57 patients)



Dose Level (mg)	50	50	200	50	200	200	400	200	400	100	400	400
Baseline SLD (mm)	68	35	52	315	122	75	41	100	83	46	47	73
Days on Treatment	19	38	92	34	40	91	80	42	255	345	127	180
Active on Treatment	N	N	N	N	N	N	N	N	N	Y	N	Y

Dose Level (mg)	200	400	100	400	400	400	400	400	400	400	200	400
Baseline SLD (mm)	34	86	48	34	62	54	106	104	85	107	35	99
Days on Treatment	346	123	165	61	543	199	126	71	85	42	126	93
Active on Treatment	Y	Y	N	Y	Y	N	N	Y	Y	Y	N	N

Dose Level (mg)	400	400	400	400	200	400	100	100	400	200	400	400
Baseline SLD (mm)	75	66	11	53	22	102	130	41	23	82	119	15
Days on Treatment	100	256	143	147	252	150	417	514	265	116	207	274
Active on Treatment	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y

Dose Level (mg)	50	200	400	400	200	400	100	400	400	400	400	400	400
Baseline SLD (mm)	50	41	51	196	10	30	21	142	101	32	31	21	49
Days on Treatment	303	293	199	64	453	72	359	166	119	143	95	276	388
Active on Treatment	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y

8 of 57 patients are not represented in waterfall plot, n=1 discontinued before first tumor assessment and n=7 ongoing without first tumor assessment by CCOD. All 8 patients treated with 400mg QD.

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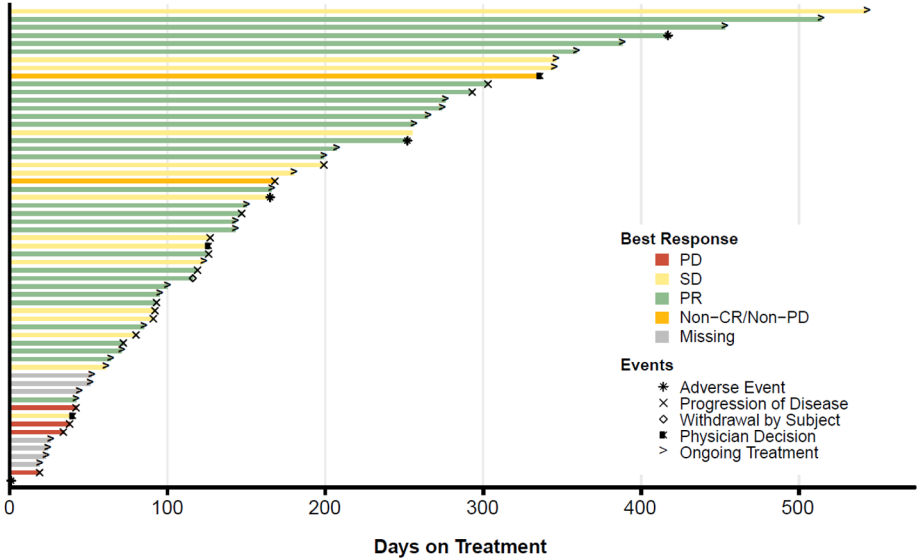
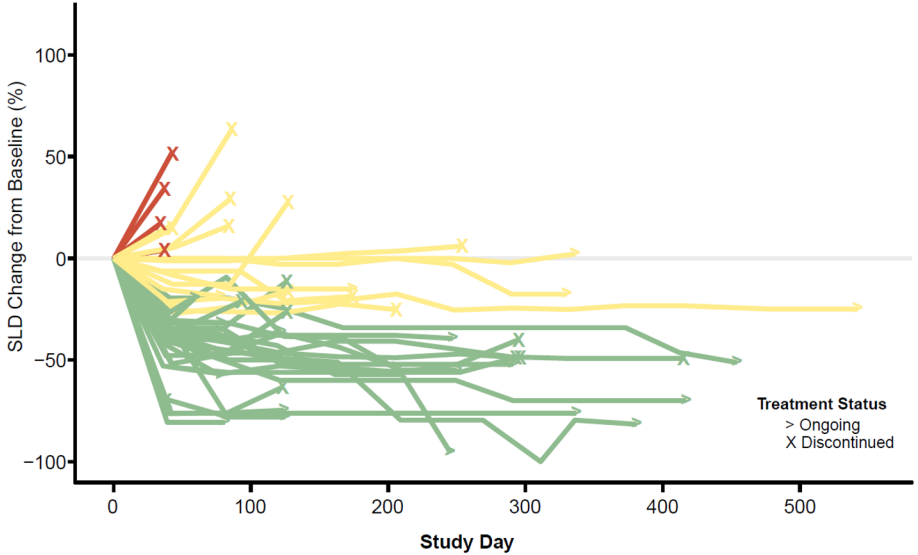
Antitumor activity: NSCLC

Time on study treatment, best response, and reason for treatment discontinuation N=59

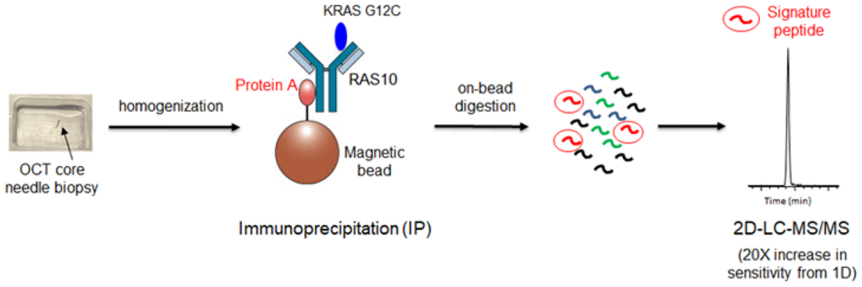


Percentage changes in sum of tumor diameters over time N=57

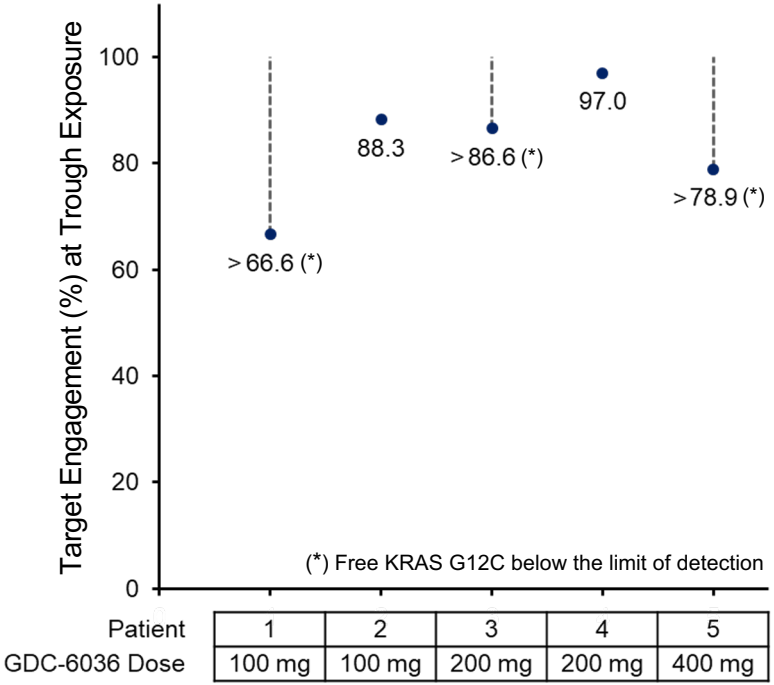


Target engagement: NSCLC

Quantitative assessment of KRAS G12C target engagement



$$\%\ \text{Target engagement} = \frac{\text{Alkylated KRAS G12C}}{\text{Alkylated KRAS G12C + Free KRAS G12C}} \quad \text{Total KRAS G12C}$$



Patient	1	2	3	4	5
GDC-6036 Dose	100 mg	100 mg	200 mg	200 mg	400 mg

Conclusions

- GDC-6036 demonstrated an **acceptable safety profile** with manageable, tolerable, and reversible adverse events across tumor types
- The PK profile of GDC-6036 is **compatible with once-daily dosing**
- **High KRAS G12C target engagement** was observed in NSCLC tumors
- Monotherapy GDC-6036 has **encouraging anti-tumor activity** in previously treated NSCLC patients with *KRAS G12C* mutation

GDC-6036 Development

- GDC-6036 is also being investigated in combination with other anti-cancer therapies in this study:

GDC-6036 + atezolizumab	GDC-6036 + cetuximab	GDC-6036 + bevacizumab	GDC-6036 + erlotinib	GDC-6036 + GDC-1971 (SHP2 inhibitor)	GDC-6036 + inavolisib (PI3K alpha inhibitor)
NSCLC	CRC	SOLID TUMORS	NSCLC	SOLID TUMORS	SOLID TUMORS

- A **Phase II/III study** is recruiting NSCLC patients for treatment with GDC-6036 vs. docetaxel (**BFAST;** NCT03178552)

www.clinicaltrials.gov/ct2/show/NCT03178552

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