Trial in Progress: Phase 1 study of BI 1823911, an irreversible KRAS^{G12C} inhibitor targeting KRAS in its GDP loaded state, as monotherapy and in combination with the pan-KRAS SOS1 inhibitor BI 1701963 in solid tumours expressing KRAS^{G12C} mutation

#2667

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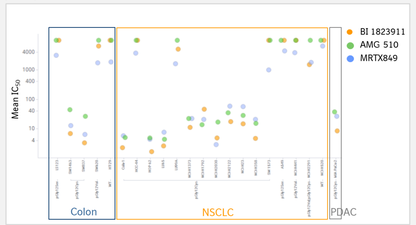
Introduction

- KRAS^{G12C} mutations are predominantly found in non-small cell lung cancer (NSCLC, 13%), in colorectal cancer (CRC, 3%), and with a lower prevalence of 1% in pancreatic ductal adenocarcinoma (PDAC). The amino acid exchange at position 12 from glycine to cysteine renders RAS insensitive to GAP-catalyzed hydrolysis but not to intrinsic hydrolysis and consequently, KRAS^{G12C} is still dependent on GEF stimulation to achieve full activation. The active GTP–loaded form of KRAS^{G12C} is favored and leads to activation of downstream signaling and proliferation. Covalent KRAS^{G12C} inhibitors binding to the inactive GDP-KRAS^{G12C} form block KRAS^{G12C} mediated signaling and induce apoptosis. The therapeutic impact in non-small cell lung cancer (NSCLC) whose tumors carry this mutation was demonstrated clinically by sotorasib (AMG 510) and adagrasib (MRTX849) leading to approval of sotorasib in KRAS^{G12C} mutant NSCLC.
- However only a fraction of patients is initially responding and patients who achieved an objective response ultimately progressed on-treatment. It became clear from these studies that KRAS^{G12C} inhibitors require a combination partner to either achieve a deeper response initially or to prevent development of resistance.
- The KRAS^{G12C} inhibitor BI 1823911 is more potent compared to sotorasib or adagrasib and showed comparable in vivo efficacy at a dose of 60 mg/kg vs. 100 mg/kg of either sotorasib or adagrasib in preclinical studies. The pan-KRAS SOS1 inhibitor BI 1701963 is the first direct KRAS signaling modifier, which entered phase I clinical trials both as a monotherapy as well as in combination with KRAS^{G12C} inhibitors, MEK inhibitors and irinotecan. Pan-KRAS SOS1 inhibitors exhibit activity against a broad spectrum of KRAS alleles, including the major G12D/V/C and G13D oncoproteins, while sparing the interaction of KRAS with SOS2. In the presented combination concept BI 1701963 shifts the balance of KRAS^{G12C} to its GDP-loaded form, which is the state to which BI 1823911 covalently binds to. Vertical pathway inhibition with BI 1823911 and BI 1701963 shows enhanced pathway modulation and synergistic anti-tumor effects.
- These results supported the start of a phase I trial, investigating the safety, tolerability, recommended dose and preliminary efficacy of BI 1823911 alone and in combination with the pan-KRAS SOS1 inhibitor BI 1701963. The trial includes cohorts of patients with KRAS^{G12C} mutant solid tumors, such as NSCLC, CRC, cholangiocarcinoma, and pancreatic adenocarcinoma, both KRAS therapy naïve or KRAS therapy relapsed. The first patients in the trial were treated in the monotherapy arm, dose escalation started at a dose of 50 mg. Primary endpoints include dose-limiting toxicities, treatment-emergent or -related adverse events. Secondary endpoints include pharmacokinetic properties of combination regimens and preliminary efficacy.

Anti-proliferative Activity of BI 1823911

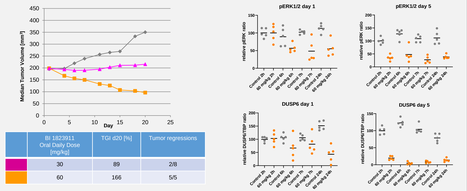
Figure 1: BI 1823911 is a potent and selective KRAS^{G12C} inhibitor with higher anti-proliferative activity compared to AMG 510 or MRTX849



BI 1823911, AMG 510 and MRTX849 were dose titrated in a panel of either KRAS^{G12C} mutant or non-KRAS^{G12C} mutant colon cancer, NSCLC or PDAC cell lines. After five days of incubation cell viability was determined using Cell-Titer-Glo® as read-out (3 days - NCI-H441, NCI-H2122). Mean IC_{50} of ≥2 biological replicates are shown.

In vivo PD Modulation and Efficacy for BI 1823911

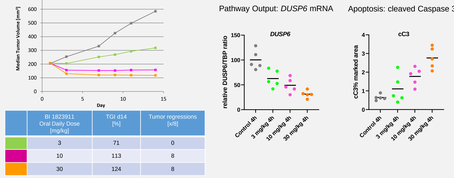
Figure 2: NSCLC KRAS^{G12C} cell line derived xenograft – NCI-H358



	BI 1823911 Oral Daily Dose [mg/kg]	TGI d20 [%]	Tumor regressions
	30	89	2/8
	60	166	5/5

Two doses of BI 1823911 were used for the treatment of NCI-H358 tumor bearing mice. 30 mg/kg led mainly to tumor stasis whereas 60 mg/kg led to regressions. PD analysis of such tumors after 1 and 5 days of treatment demonstrate consistent and durable PD modulation (pERK/MSD or DUPS6 mRNA/quantigene).

Figure 3: Pancreatic cancer KRAS^{G12C} cell line derived xenograft – MIA PaCa-2

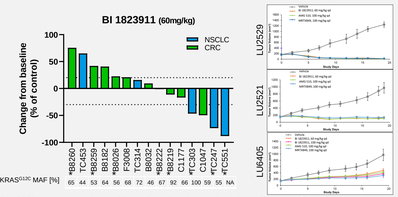


	BI 1823911 Oral Daily Dose [mg/kg]	TGI d14 [%]	Tumor regressions [x/6]
	3	71	0
	10	113	8
	30	124	8

Dose dependent efficacy (3, 10 and 30 mg/kg), PD modulation (DUSP6 mRNA, quantigene, 4h post single dose) as well as disease marker modulation (cleaved Caspase 3, IHC, 4h post single dose) were observed in MIA PaCa-2 model.

In vivo Efficacy of BI 1823911 on PDX Models

Figure 4: Anti-tumor activity on KRAS^{G12C} mutant NSCLC and CRC mouse xenograft models



Left: BI 1823911 was dosed with 60 mg/kg daily with a schedule of 5 days on/2 days off or qd (*). Change from baseline calculated according to Hallin et al., Cancer Discovery, 2020, showing a spread of anti-tumor activity across models, available genetic markers did not reveal a correlation to response (data not shown). PDX – patient derived xenograft; MAF – mutant allele frequency.
Right: BI 1823911, AMG 510 and MRTX849 tested in three NSCLC PDX models showing comparable efficacy.

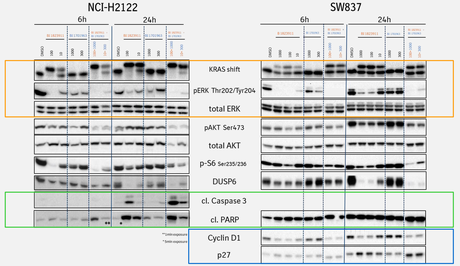
Screening for Combination Partners with BI 1823911

Figure 5: BI 1823911 shows good synergistic anti-proliferative activity in combination with PI3K/mTOR, EGFR inhibitors, and also SOS1 inhibitor

Ten KRAS^{G12C} and five non-KRAS^{G12C} cell lines were treated with BI 1823911 in combination with listed combination partners, anti-proliferative activity was determined after five days of incubation using Cell-Titer-Glo®. Heat maps shows synergy scores based on Loewe additivity.

In Vitro Pathway Modulation by KRAS^{G12C} + SOS1 Inhibition

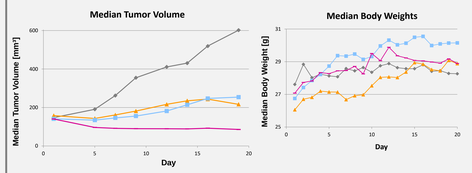
Figure 6: Deepened PD modulation when BI 1823911 is combined with SOS1i BI 1701963



KRAS^{G12C} NSCLC and CRC cell lines, NCI-H2122 and SW837, respectively, were treated with indicated compounds and concentrations for 6 or 24h, cell lysates were analysed by immunoblotting with indicated antibodies.
Markers within MAPK pathway (KRAS, p-ERK/ERK, DUSP6) are shown in orange, G1 cell cylce markers (Cyclin D1, p27) in blue, apoptosis marker (cleaved caspase 3, cleaved PARP) in green.

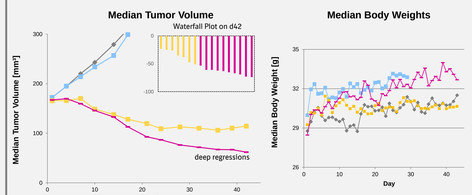
In vivo Efficacy of KRAS^{G12C} and SOS1 Inhibitor

Figure 7: Synergistic anti-tumor activity in NSCLC tumor model – NCI-H2122



NCI-H2122		Dose [mg/kg]	Schedule & Route		TGI d19 [%]	Tumor regressions [x/x]
Natrosol		--	qd	po	--	0/8
BI 1823911		60	qd	po	87	1/8
BI 1701963 (SOS1)		50	bid	po	75	0/8
BI 1823911 BI 1701963 (SOS1)		20 50	qd bid	po po	112	9/9

Figure 8: Anti-tumor activity in CRC tumor model – SW837



SW837		Dose [mg/kg]	Schedule & Route		TGI d42 [%]	Tumor regressions [x/x]
Natrosol		--	qd	po	--	0/7
MRTX849		100	qd	po	108	7/7
BI 1701963 (SOS1)		50	bid	po	--	0/10
MRTX849 BI 1701963 (SOS1)		100 50	qd bid	po po	117	10/10

NMRI nude nice (Taconic) were injected with NCI-H2122 or SW837 cells subcutaneously. Mice were randomized into groups 16 days (NCI-H2122) or 28 days (SW837) after cell injection. Tumor diameter were measured three times a week and body weight was measured daily. Mice were dosed orally with Natrosol as control (qd), BI 1823911 (60 mg/kg, qd) or MRTX849 (100 mg/kg, qd), BI 1701963 (50 mg/kg, bid) or a combination of BI 1823911 (dose adjusted to 20 mg/kg, qd) and BI 1701963 or MRTX849 and BI 1701963.

Mouse Clinical Trial - KRAS^{G12C} and SOS1 inhibitor

Figure 9: Deeper response upon combination of BI 1823911 or MRTX849 with SOS1 inhibitor in CRC PDX/CDX models

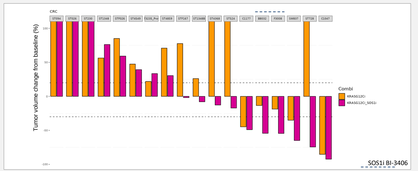
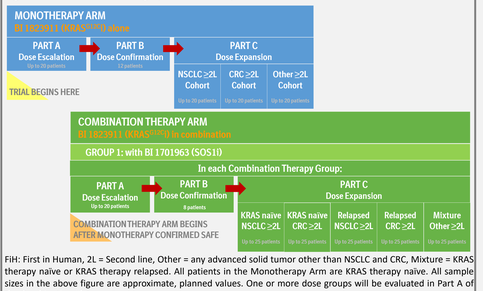


Figure shows efficacy data from mouse clinical trials (14 models, 1 mouse/treatment/model) or conventional CDX or PDX models (with 5-10 mice/group) combining either BI 1823911 (60 mg/kg qd in monotherapy, dose adjusted in combination to 20 mg/kg qd) or MRTX849 (100 mg/kg, qd) with a SOS1i (BI 1701963 or BI-3406, 50 mg/kg bid). Plot represents strongest tumor volume change from baseline following at least 14-day treatment.

Phase I FiH Clinical Trial - BI 1823911 and BI 1701963

Figure 10: Phase 1 Trial Design (NCT04973163)



FiH: First in Human, 2L = Second line, Other = any advanced solid tumor other than NSCLC and CRC, Mixture = KRAS therapy naïve or KRAS therapy relapsed. All patients in the Monotherapy Arm are KRAS therapy naive. All sample sizes in the above figure are approximate, planned values. One or more dose groups will be evaluated in Part A of the Combination Therapy Arm.

Key Findings and Conclusions

- BI 1823911 is a selective and potent KRAS^{G12C} inhibitor and *in vivo* efficacy at 60 mg/kg is comparable to 100 mg/kg AMG 510 or MRTX849.
- Combination of BI 1823911 with SOS1 inhibitor BI 1701963 shows increased, sustained PD modulation and deeper anti-tumor efficacy.
- Across a panel of NSCLC and CRC CDX or PDX models the combination of a KRAS^{G12C} inhibitor with a SOS1 inhibitor showed added benefit, and the data support phase I study (NCT04973163).

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