Preclinical and emerging Phase 1 study data indicates that novel deuterated MET kinase inhibitor DO-2 mitigates the side effects seen with current approved MET kinase inhibitors : Preventing deleterious 'de-hinging' to improve tolerability

Poster C152

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Background: MET is a clinically validated drug target

MNNG HOS transforming gene (MET) kinase inhibitors have demonstrated clinical activity in patients with non-small cell lung cancer (NSCLC) harboring exon14 (METex14) skipping mutations, validating this as an actionable drug target[1]. High daily doses (500-800mg daily) are needed to reach sufficient plasma exposure of active drug to achieve sufficient target engagement to drive efficacy. However, these high doses are associated with toxicities that frequently lead to dose interruptions and reductions which negatively impact efficacy[2].

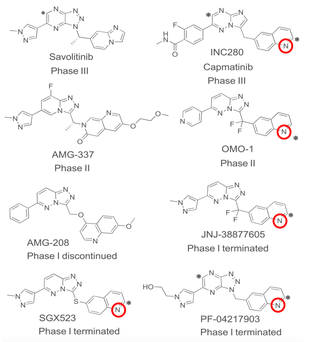
JNJ-38877605 (DO-0) was one of the first selective Type 1B MET kinase inhibitors to enter the clinic in 2008 (NCT00651365). The highest dose tested in this study (60mg) caused grade 1 creatinine increases in 5/5 patients leading to termination of the study as exposures were below predicted efficacious levels[3]. JNJ-38877605 was subsequently shown to undergo metabolism by a species-specific aldehyde oxidase 1 into an insoluble metabolite. This same liability was reported for another selective MET kinase inhibitor (SGX-523) that resulted in the termination of this agent. The same metabolic liability has since been found in more members of this class of MET inhibitors[4].

DO-2 is the first selective MET kinase inhibitor that has been specifically engineered using deuterium to block this metabolic liability in order to reduce toxicity and increase efficacy.

Limitations of current MET kinase inhibitors

The liver enzyme aldehyde oxidase (AOX) leads to unwanted metabolic breakdown resulting in inactive and toxic metabolites

Frequent or high dosing to attain a sufficiently high plasma level of active drug resulting in significant side-effects, dose reductions and interruptions



Many of the current generation of selective MET kinase inhibitors share a similar chemical scaffold.
They adopt the same Type 1B binding mode with π stacking interaction with Tyr1230.
The Nitrogen (O) adjacent to the AOX-1 metabolic site (*) is critical for binding to the target.
AOX-1 replaces the Hydrogen on the metabolic site * by a bulky substituent which prevents binding to target - "De-Hinging" [5] results in:

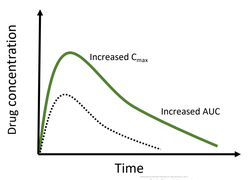
- loss of activity on MET
- altered phys/chem properties of metabolite including precipitation due to lower solubility

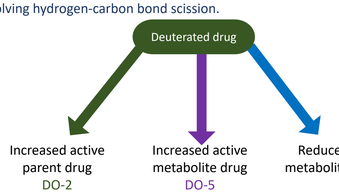
Current competitor agents carry metabolic liabilities that result in reduced exposure to active parent drug.
Most abundant metabolite(s) of parent drug with no or negligible pharmacological activity for:

- Capmatinib[6] = 50%
- Tepotinib[7] = 65%
- Savolitinib[8] = 88%

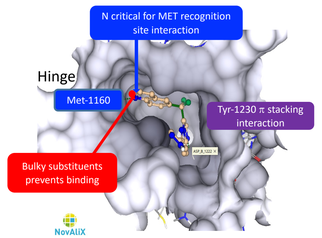
Deuteration, small chemical change, big impact

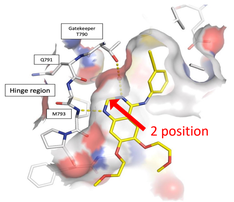
Deuterated drug: a small molecule in which one or more of the hydrogen atoms are replaced by deuterium.
As deuterium and hydrogen* have nearly the same physical properties, deuterium substitution is one of the smallest structural changes that can be made to a molecule[9].
"Deuterium-carbon" bonds are 6 to 10 times more stable than the corresponding "hydrogen-carbon" bonds, slowing the rate of bond cleavage: Kinetic Deuterium Isotope effect (KDIE) which impacts the biological fate of drugs that are metabolized by pathways involving hydrogen-carbon bond scission.





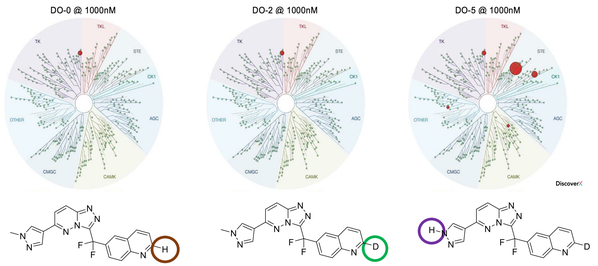
Bulky substituents at critical 2 position of type 1 kinase inhibitors results in "de-hinging" and loss of inhibitory activity





Hillig et al www.pnas.org/lookup/suppl/doi:10. 1073/pnas.1812963116

DO-0, DO-2 and DO-5 have similar inhibitory potency to other competitors against MET related kinases and MET driven cell lines



Non-deuterated parent (DO-0/JNJ-38877605) — DO-2 — Active metabolite (DO-5)

Kd determination for active kinases identified during broad profiling

Target	capmatinib	DO-2	DO-5
Gene Symbol	Kd (nM)	Kd (nM)	Kd (nM)
HASPIN	480	1200	140
MELK	>10000	>10000	4300
MET	0.2	0.2	0.2
MET(M1250T)	0.5	1.6	0.4
MET(Y1235D)	0.5	4.4	2.4
MYLK	9900	8300	290
PIPSK2C	9800	650	450
YSK4	1300	2300	80

DiscoverX

Cellular IC_{50} determination in sensitive (MET exon 14) and resistant (ras mutant) models

	Cell line IC_{50} (nM)		
Compound	Hs746T	NCI-H441	SW837
DO-2	21	>15800	>15800
DO-0	14	>15800	>15800
DO-5	15	>15800	>15800
capmatinib	14	8210	5748
crizotinib	5	1765	1335
savolitinib	13	4467	>15800
tepotinib	8	3009	3298

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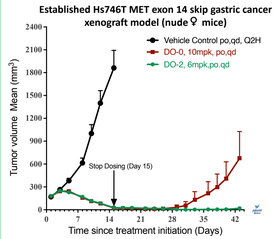
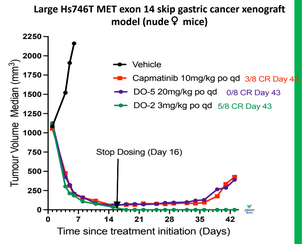
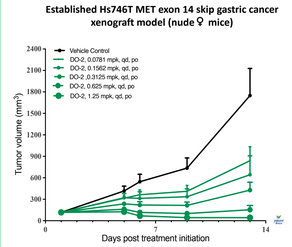
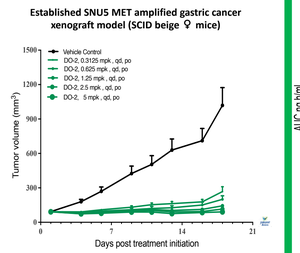
DO-2 is more active in vivo than DO-0, DO-5 or capmatinib



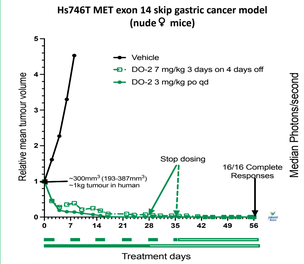


Dose dependent inhibition of MET exon14 skip and MET amplified xenograft tumours

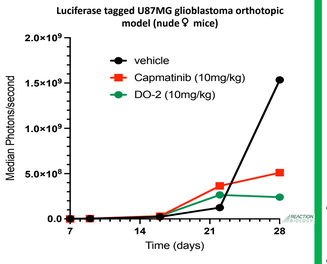




Elimination of tumours in 16/16 animals at 3mg/kg daily or 7mg/kg '3 days on 4 off'



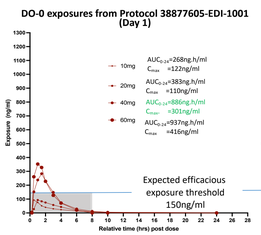
DO-2 is Brain penetrant ($K_{p,uu,brain}$ 0.3) and shows efficacy in orthotopic tumour model

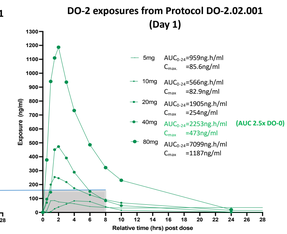


No Significant Alerts observed in rabbit 28 day tolerance study up to 40mg/kg

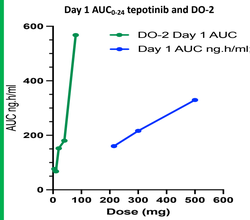
		vehicle	20mg/kg		40mg/kg (NOAEL)	
			DO-2	DO-5	DO-2	DO-5
C_{max} ng/ml	D1		800	675	4500	2782
Exposure	D28		1412	1239	5022	3507
AUC ng.h/ml	D1		1576	1415	7810	5501
n=6	D28		2572	2572	9433	7559
Mortalities		none	none	none	none	none
Day 28 tissue weights (g)			Male	Female	Male	Female
Liver (SD)		64.77 (6.22)	64.98 (4.32)	74.84 (16.45)	64.77 (10.06)	64.33 (5.73)
Adrenals (SD)		0.309 (0.06)	0.32 (0.07)	0.26 (0.05)	0.29 (0.05)	0.29 (0.02)
Spleen (SD)		0.96 (0.51)	0.81 (0.26)	1.30 (0.56)	1.37 (0.82)	1.18 (0.26)
Thymus(SD)		2.91 (0.71)	2.69 (0.38)	0.14 (0.05)	3.21 (0.36)	3.67 (0.75)
Fasting (SD)		2590.20 (158.31)	2406.23 (88.47)	2656.17 (206.85)	2510.73 (77.78)	2768.87 (122.33)

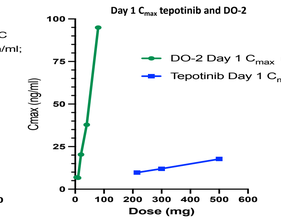
Clinical exposures of DO-2 are significantly higher than seen with DO-0



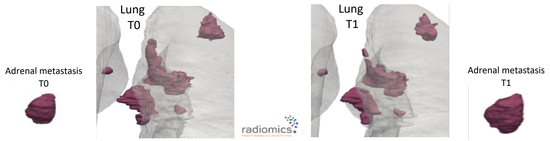


Clinical exposures of DO-2 are higher than seen with tepotinib at its RP2D





Early signs of clinical activity for DO-2 with 20mg dose of DO-2 resulting in ~20% reduction in tumour volume : ~10g drop in tumour weight ~1 billion cells killed



Lesion		Lung (7)		Adrenal (1)		Combined	
T0 (28/06/2023)		42.3 cm³		4.46 cm³		46.76 cm³	
T1 (24/08/2023)	T1-T0/T0	31.07 cm³	-26,5%	5.99 cm³	34%	37.06 cm³	-20.8%

Summary

- DO-2 is the first deuterated MET kinase inhibitor to enter the clinic. DO-2 has been re-engineered to block a metabolic liability that resulted in the formation of an inactive and poorly soluble metabolite(s) associated with renal adverse events.
- This metabolic liability is shared with other type 1B competitor agents.
- Pre-clinical efficacy data against MET exon 14 skipping and MET amplified xenograft models has identified the minimum effective dose to be 0.2mg/kg (NCI guidelines) whilst doses <1mg/kg caused tumour regression.
- 'Time over threshold' (ToT: 150ng/ml) for 6-8hrs was sufficient to achieve tumour regression in MET exon14 skipping and MET amplified xenograft models. 24/7 target shutdown was not found to be required with DO-2.
- Based on differences in plasma protein binding (12% free in mouse vs 8% free in human) the target exposure in the clinic was defined to be 160ng/ml for 6-8hrs.
- This exposure threshold has now been exceeded and encouraging early signs of clinical efficacy activity, including tumour volume reduction and a good safety profile are consistent with a 're-engineered' MET-inhibitor with a better pharmacological benefit risk ratio profile.
- The ongoing study (NCT05752552) continues to accrue patients identified to have known activating MET pathway alterations.