Preliminary Safety and Pharmacokinetics of the MET-TKI DO-2 in Patients with Advanced Solid Tumors Harboring MET Aberrations: A Phase I Study

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Poster 143

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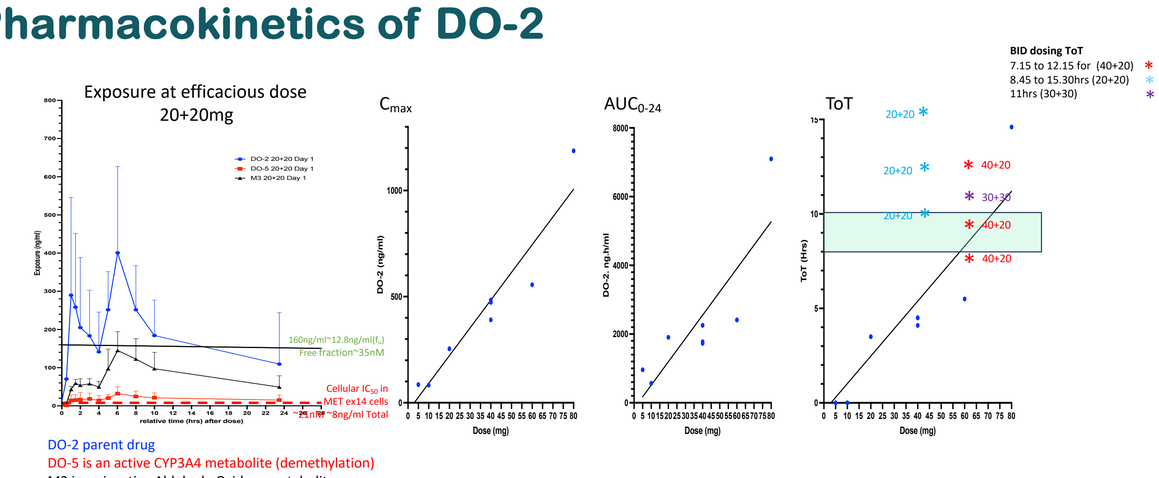
Introduction

- DO-2 is a highly selective type 1B MET TKI re-engineered to block a metabolic liability using selective deuterium replacement.
- Activating mutations of MET kinase including the exon14 skipping mutation result in oncogenic signalling via overexpression of wtMET receptor on tumour cells.
- The degree of inhibition of MET signalling on tumour cells will be matched by 'on target' inhibition of physiological MET signalling.
- DO-2 has 'fast on' and 'fast off' binding kinetics on MET (see poster 407), that results in target inhibition being directly correlated with plasma exposure.
- Preclinical data indicate that maintaining >95% MET target inhibition for 8-10 hours is required and sufficient to drive complete regression of MET driven xenograft models.
- The minimum effective dose in mice is <0.3mg/kg and efficacy correlated with achieving the required time over threshold (ToT) and not AUC_{0-24} or C_{max}
- DO-2 clinical exposure above 160 ng/mL for 8-10hrs (ToT) predicted to drive clinical efficacy.
- Here, we report promising preliminary findings from a first-in-human phase I trial (NCT05752552) of DO-2 in patients with advanced solid tumors harboring MET aberrations, aiming to determine pharmacokinetics, safety and the recommended phase 2 dose (RP2D).

Pharmacokinetics of DO-2



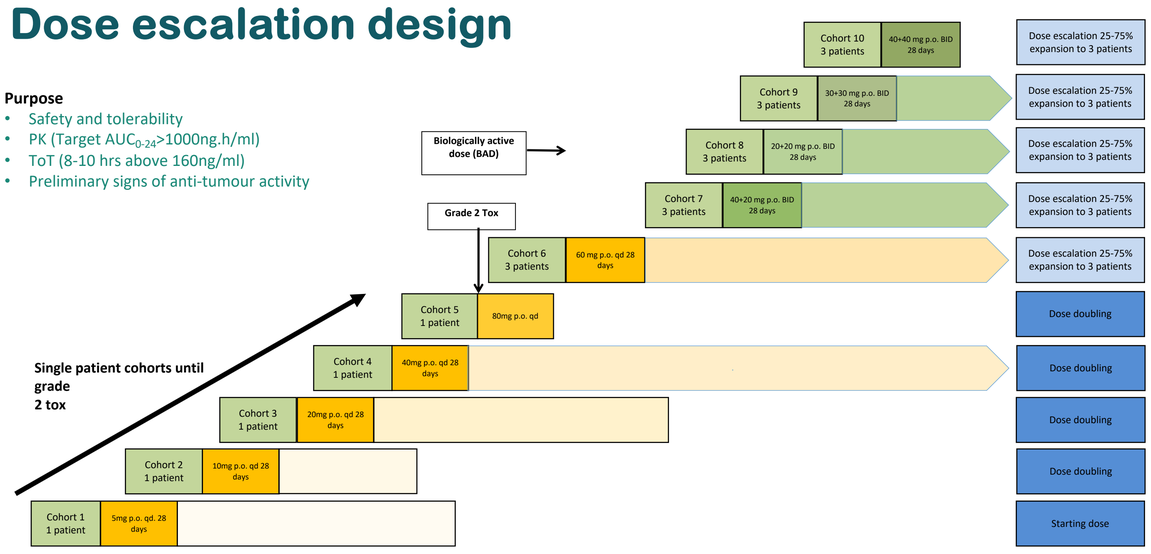
DO-2 parent drug
DO-5 is an active CYP3A4 metabolite (demethylation)
M3 is an inactive Aldehyde Oxidase metabolite (Oxidation) that can be further metabolized to form a further metabolite (M5)

- Dose dependent increase in C_{max} and AUC with QD dosing
- ToT exceeded with BID dosing without excessive C_{max}

Analyte	DO-2							
Dose (mg)	5	10	20	40	40	40	60	80
T_{max} (h)	1.5	4	1.43	2.0	1.5	1.6	1.4	2.1
C_{max} (ng/mL)	85.6	82.9	254	473	391	484	556	1187
AUC_{0-24} (ng.h/mL)	959	566	1905	2253	1730	1774	2412	7099
ToT hrs over 160ng/ml	0	0	4	4.5	4.1	4.5	5.5	14.6

Dose escalation design

Purpose
- Safety and tolerability
- PK (Target AUC_{0-24}>1000ng.h/ml)
- ToT (8-10 hrs above 160ng/ml)
- Preliminary signs of anti-tumour activity



Key eligibility criteria

- Proven MET activating mutations or MET amplification (≥ 10 copies) at diagnosis, recent confirmation of MET positivity (tissue or blood) not required at entry
- No longer eligible for approved, available standard therapies
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

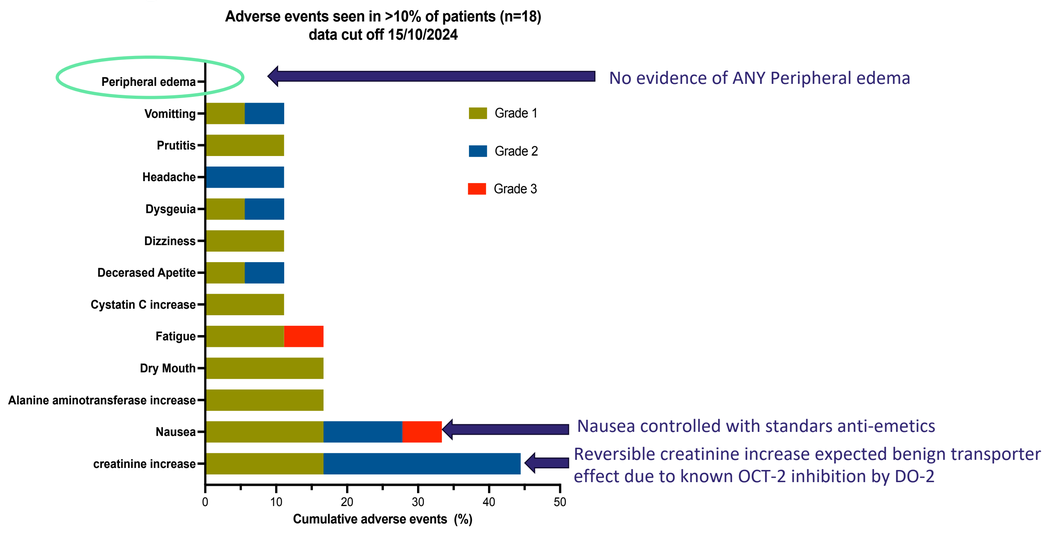
Eligible patients received DO-2 once or twice (4hr interval) daily (QD/BID) orally, under fasting conditions.

- Primary endpoint: safety and tolerability.
- Secondary endpoints: pharmacokinetics and anti-tumor activity.
- Dose-escalation:
  - Simon stage 3 accelerated titration design ("1+1")
  - Starting at 5mg QD, until grade 2 toxicity.
  - Thereafter, a "3+3" design.
- Response assessment was performed every 7-8 weeks.

Patient demographics

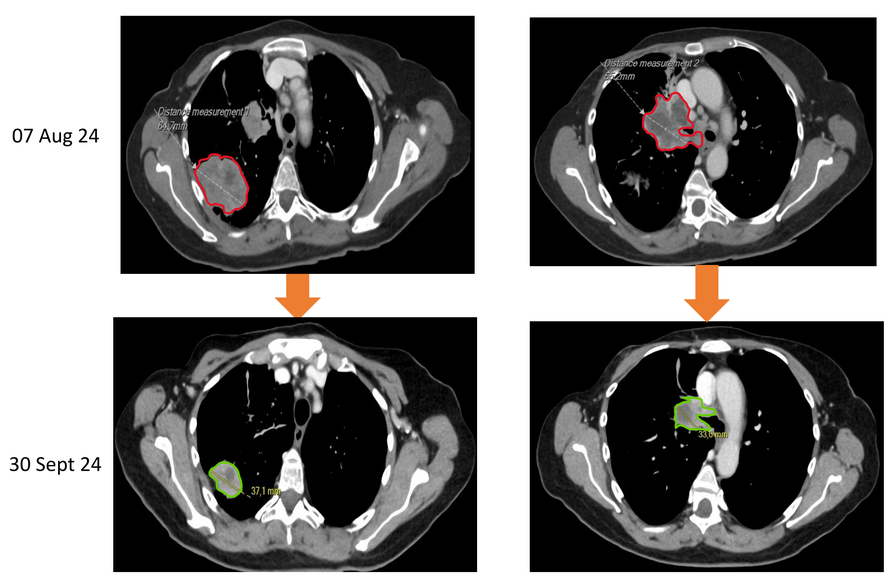
Median Age, years (range)	68 (49-77)
Male	13
Female	5
Lung Carcinoma	15
Gastric cancer	1
Kidney Carcinoma	1
Ovarian Carcinoma	1
Stage III	1
Stage IIIB	3
Stage IV	10
Stage IVa	2
Stage IVb	2
MET exon 14 skipping mutation	12
MET amplification positive >10 fold	4
MET activating mutation positive (other than exon 14)	1
Other MET mutation	1
No previous anti-cancer treatment (DO-2 First line)	3
Previously treated with systemic treatment	15
Patients with Measurable Lesions	14
Patients with Non-Measurable Lesions only	3
Unknown	1

Safety of DO-2

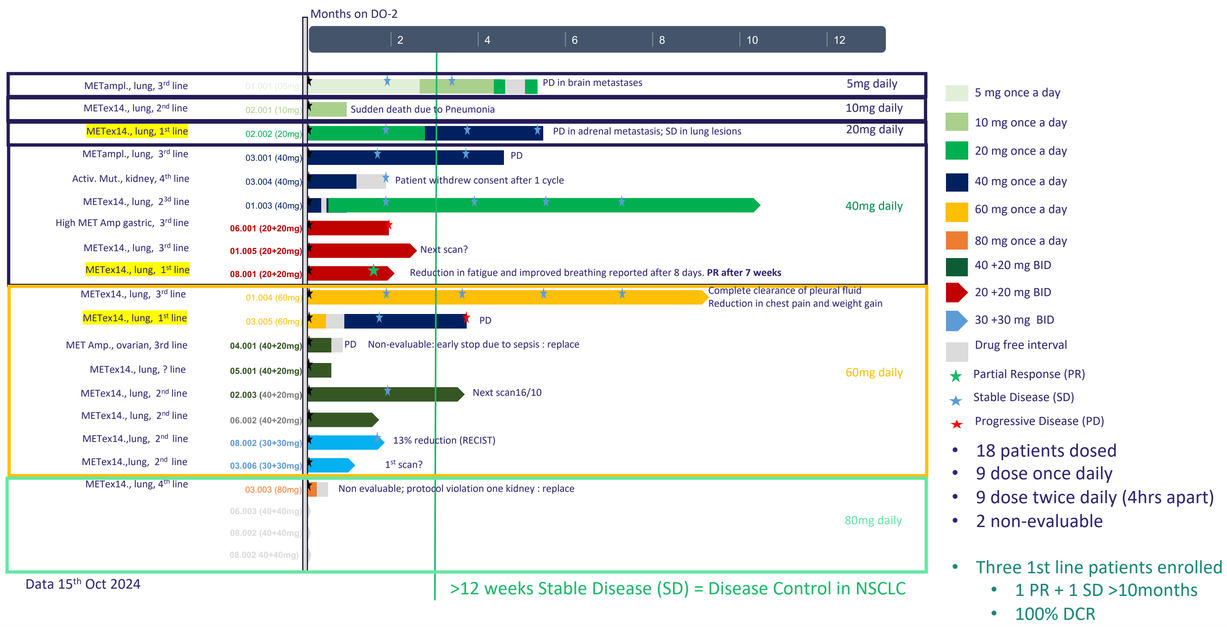


- Reversible creatinine increase seen in 8/18 patients
- No 'on target' peripheral edema seen
- No liver enzyme elevations seen

Preliminary clinical activity



RECIST 1.1
Partial Response (↓39%)



- 18 patients dosed
- 9 dose once daily
- 9 dose twice daily (4hrs apart)
- 2 non-evaluable

- Three 1st line patients enrolled
  - 1 PR + 1 SD >10months
  - 100% DCR

Conclusions

- DO-2 is well tolerated at doses up to 60mg QD and 40+20mg BID (4h interval) with no evidence of peripheral edema.
- Reversible creatinine increases (grade 1 and 2) seen in 8/18 patients.
- Partial response (↓39%) seen in 1 patient at 20+20mg and further encouraging signs of clinical benefit, including prolonged (>9 months) disease control observed
- BID dosing (30+30 and 40+40mg) is currently being evaluated.
- Expansion cohorts in patients confirmed to have fresh MET mutation data is foreseen

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The first author has no disclosures of interest.

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