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#928P

Safety and activity of the MET-TKI DO-2 in patients with advanced solid tumors: Phase I Study

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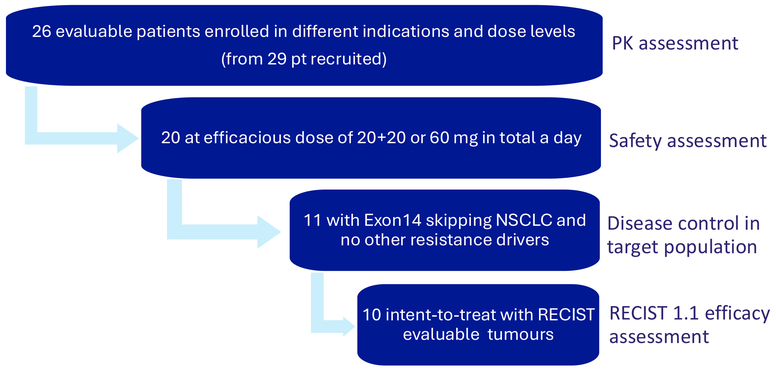
Background

- DO-2 is a potent, highly selective, deuterated type IB MET tyrosine kinase inhibitor (Kd 0.2 nM; >3000-fold selectivity vs. 450+ kinases).
- Designed with 'fast on' / 'fast off' binding kinetics, making MET inhibition directly dependent on plasma exposure and time over threshold (ToT).
- Preclinical models demonstrated that maintaining >95% MET inhibition for 8-10 hours is sufficient for efficacy, without requiring 24/7 continuous inhibition.
- The 'oncogenic' form of the MET kinase (e.g., exon 14 skipping mutation, amplification) retains a wild-type kinase domain but drives aberrant signaling due to impaired receptor internalization or increased copy number.
- Continuous inhibition of physiological MET signaling is associated with "on-target" toxicities such as peripheral edema, reported in >50% of patients on other MET inhibitors
- DO-2 has been developed to achieve deep, cyclic MET inhibition to overcome oncogene addiction while minimizing on-target toxicity.
- Here, we present pharmacokinetics, safety, and preliminary efficacy from the dose escalation part of the first-in-human phase I trial in patients with advanced solid tumors harboring MET aberrations (NCT05752552).



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

Patient demographics

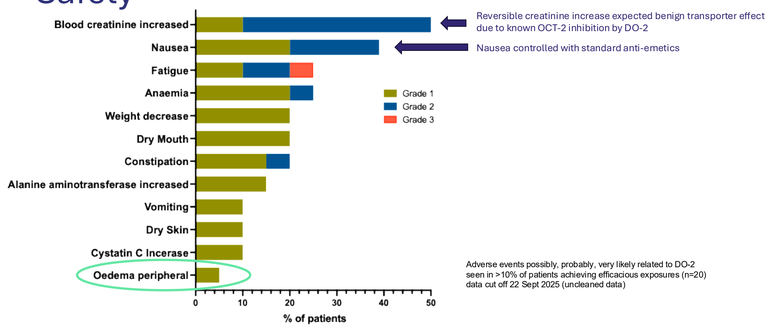
Median Age, years (range)	68 (47-77)
Male	18
Female	11
Lung Carcinoma	25
Kidney Carcinoma	1
Ovarian Carcinoma	1
Gastro-oesophageal junction	1
Rectal Carcinoma	1
MET exon 14 skipping mutation	21
MET amplification positive >10 fold	6
MET activating mutation positive (other)	1
Other MET mutation	1
0 line of systemic pre-treatment	11
1 line of systemic pre-treatment	9
2 lines of systemic pre-treatment	4
No previous anti-cancer treatment	7
Previously treated with radiotherapy only	4
Previously treated with systemic treatment	18
Patients with Measurable Lesions	26
Patients with Non-Measurable Lesions only	3

Data cut-off 11-Aug-2025 (uncleaned data)

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:** Every 7-8 weeks

Safety

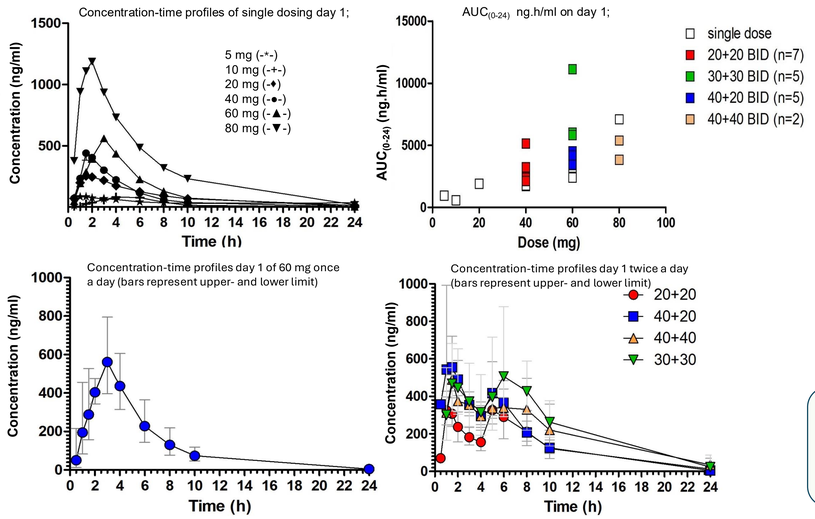


- TRAEs were mainly grade 1 or 2
- edema, commonly associated with MET inhibition, was seen in only 1 patient
- Reversible Increases in serum creatinine was the most frequent adverse event, with only 1 grade 3 TRAE seen.
- One patient had nausea that caused dehydration leading to a creatinine increase, prior to being well controlled with standard anti-emetics.
- Grade 3 TRAES occurred in 18% of patients

DO-2 @ Efficacious exposure(s) at 20+20mg and 60mg daily dose (N=20)		
Adverse event	**Any Grade n (%)**	**Grade 3+4 n (%)**
Peripheral oedema	1 (5)	-
Nausea	6 (30)	-
Vomiting	2 (10)	-
Blood creatinine increase	11 (55)	1 (5)
Dyspnoea	-	-
Fatigue	4 (20)	1 (5)
Decreased appetite	1 (5)	-
Alanine aminotransferase increase	3 (15)	-
Lipase increased	-	-
Diarrhoea	1 (5)	-
Hypoalbuminemia	-	-
Dose interruption due to adverse event(s)	5 (25)	
Dose reduction due to adverse event(s)	2 (10)	
Discontinuation due to adverse event(s)	2 (10)	

eCRF output 22 Sept 2025. (uncleaned data). AEs related (possibly, probably, very likely related)

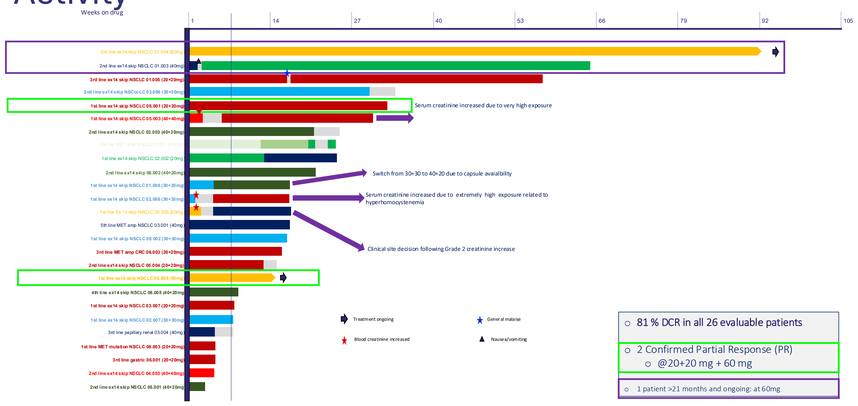
Pharmacokinetics



Conclusions

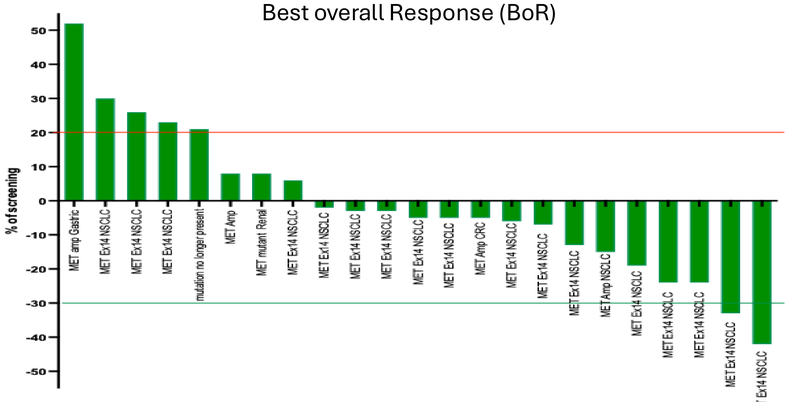
- DO-2 was well tolerated. MTD was not declared.
- Peripheral edema, observed in up to 80% of patients treated with competitor agents of this class, was only seen in one patient who had an 'outlier' PK profile that resulted in DO-2 exposures indicative of continuous MET inhibition.
- Reversible creatinine increase was the main biomarker change seen at dose levels that reached the preclinically defined Time over Threshold. This transporter effect has been seen with many other TKI's and could be considered as a biomarker of DO-2 tissue exposure exceeding efficacious levels.
- PK analysis of DO-2 reveals dose dependent increase in C_{max} and AUC and sufficient ToT with BID dosing. (Food effects on DO-2 pharmacokinetics is presented in poster 995P)
- 2 out of 10 patients had partial responses. 3 patients had significant reduction in tumour diameters (19%, 24% and 24%) that did not reach PR.
- Expansion cohorts in patients with MET ex14 skip NSCLC is foreseen.

Activity



- Two patients without measurable disease with clearance of their pleural effusions including one who had complete elimination. One patient still continues on DO-2 for longer than 21 months: No adverse events other than a stable grade 1 creatinine increase.

Best overall Response (BoR)



- Tumour shrinkage, including two PR's (one confirmed) was seen in ex14 skip patients who did not have co-mutations known to be resistance drivers to targeted therapies and had achieved efficacious DO-2 exposure levels.

Disclosures

- The first author has no disclosures of interest.
- Timothy Perera is a shareholder in DeuterOncology
- Jaap Verweij, Florence Wastelin and Cecilia Ahlin are paid consultants working for DeuterOncology

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