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

Hans Prenen[1] MD, PhD, Rachel Galot[2] MD, PhD, Alexis Cortot[8] MD, PhD, Aurélie Swalduz[5] MD, PhD, Bernd Dekeyser[1] MD, Peter de Bruijn[3] PhD, Francois Zammit[2] MD, Jean-Pascal Machiels[2] MD, PhD, Brant Delafontaine[4] MD, Sylvie Rottey[4] MD, PhD, Ingrid Desar[7] MD, PhD, Marthe Paats[6] MD, PhD, Barend J. Sikkema[3] MD, , Florence Wastelin[9] MSc, Cecilia Ahlin[9] MD PhD, Timothy Perera[9] PhD, Jaap Verweij[9] MD, PhD, Carla van Herpen[7] MD, PhD, Debbie G.J. Robbrecht [3] MD, PhD

Correspondence: *tperera@deuteroncology.com*

Abstract ID-2859

Background

- MET is a transmembrane tyrosine kinase that has been clinically validated as a targetable oncogenic driver.
- Approved MET inhibitors have shown significant clinical benefit in the subset (~3%) of NSCLC patients having the oncogenic MET exon 14 skipping mutation that increases expression of wild type MET.
- Adverse events, including peripheral edema, the most frequently seen adverse event considered to be an 'on target' class effect, results in frequent dose interruptions, dose reductions and in some cases complete withdrawal of treatment for patients responding to treatment.
- MET kinase is known to play critical physiological functions including control of vascular tone. Continuous (24/7) inhibition of MET results in 'on target' toxicities such as peripheral edema that is reported in >50% of current agents that drive 24/7 target inhibition.
- MET inhibitors that have better safety profiles including lower incidence of peripheral edema represents an unmet medical need.
- Here we present Phase 1 dose escalation study results from an ongoing study with a deuterated MET kinase inhibitor DO-2.

Methods

Eligibility Criteria

- Confirmed MET activating mutations (NGS, WES, WTS or other genomic analysis methods). ECOG ≤1 with Normal organ functions. Patients with brain metastases could be included provided all of the following criteria were met: CNS lesions are asymptomatic and previously treated: No ongoing requirement for corticosteroids as therapy for CNS metastases: Imaging demonstrates stability of disease >28 days from last treatment for CNS metastases: No leptomeningeal involvement.

Patient Characteristics

- A total of 29 patients were included (18 males (62%), 11 females (38%)), with a median age of 68 years (range 47–77). All had histologically or cytologically confirmed advanced or refractory solid tumors and were no longer eligible for approved standard therapies. Most patients had NSCLC (25 (86%)); 18 (62%) had received prior systemic treatment, while 11 (38%) were treatment-naïve. The most common MET alteration was exon 14 skipping (21 (72%)), followed by MET amplification >10 fold (6 (21%)). Measurable lesions were present in 26 (90%) patients, while 3 (10%) had only non-measurable lesions.

DISCUSSION AND CONCLUSION

- Deuteration reduced metabolism and improved plasma exposure of DO-2 compared to the non-deuterated parent DO-0 enabling efficacious exposures being reached.
- Reversible serum creatinine increase (sCR) was the main biomarker change seen at dose levels that reached the preclinically defined Time over Threshold's. sCR increase has been shown to be mediated by drugs that inhibit Organic Cation Transporter 2 (OCT-2) and has been seen with many other TKI's including the main competitors.
- DO-2 treatment of MET exon 14 skip mutation positive patients, not having other known oncogenic drivers, resulted in tumor shrinkage as best response in 100% (12/12) of patients that achieved efficacious exposures.
- Of these, partial responses were seen in 2/10 patients confirming that 24/7 target inhibition is not required for efficacy.
- An additional 3/10 patients saw significant, 19%, 24% and 24% tumor shrinkages.
- 2 of the patients had pleural effusion (no RECIST target lesions) and saw clearance or reduction of their effusions, reduction in chest pain and stayed on drug for 14 or 20+ months.
- Peripheral edema (grade 1) was seen in one patient who had an 'outlier' PK profile that resulted in sustained (24hr) DO-2 exposures above the ToT supporting the hypothesis that continuous 24/7 MET inhibition is responsible for the edema.
- The dose escalation study suggests that DO-2 is a promising MET kinase inhibitor with clear signs of efficacy that is well tolerated for up to 20 months without evidence of peripheral edema or other significant toxicities.
- Based on the dose escalation study, 60mg once daily dosing with food was determined as the optimal regimen for the planned expansion cohort in 1st line MET ex14 skip NSCLC patients where the safety and efficacy of the selected dose can be further evaluated.

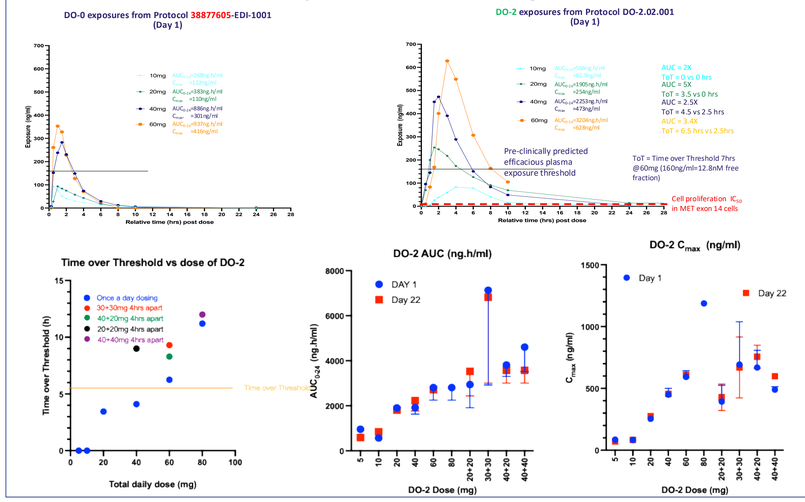
DISCLOSURES & ACKNOWLEDGEMENTS

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

Protocol DO2.22.01 NCT05752552
Study sponsored by DeuterOncology NV
www.deuteroncology.com

RESULTS

Deuteration Increases Plasma Exposure of DO-2: Extending Time over Threshold



- Deuterium incorporation resulted in significantly higher C_{max} and AUC_{0-24} and importantly ToT seen when DO-2 was dosed once a day under fasting conditions.
- No drug accumulation after 21 days of daily dosing at any of the dose levels tested.
- Switching to BID dosing 4hrs apart led to an increase in ToT compared to the same dose given once a day, whilst AUC_{0-24} values remained similar.
- BID dosing 4hrs apart under fasting conditions places an undue burden to patients, a separate healthy volunteer study showed food reduced C_{max}, increased ToT whilst keeping AUC_{0-24} unchanged (see Abstract ID-2081).

DO-2 Safety Profile is Cleaner Than Competitors with No Grade 3 or 4 Peripheral Edema

	Capmatinib (at RP2D) (N = 160)		Tepotinib (at RP2D) (N=313)		DO-2 Efficacious exposure(s) at 20+20mg and 60mg daily dose (N=20)	
	Any Grade n(%)	Grade 3+4 n(%)	Any Grade n(%)	Grade 3+4 n(%)	Any Grade n(%)	Grade 3+4 n(%)
Peripheral oedema	109 (68.1)	28 (17.5)	255 (81.5)	49 (15.7)	1 (5)	0
Nausea	72 45)	1 (0.6)	97(31)	4 (1.3)	5 (25)	-
Vomiting	4 (25.6)	1 (0.6)	45 (14.4)	4 (1)	1 (5)	-
Blood creatinine increased	119 (74.5)	1 (0.6)	184 (58.8)	4 (1)	12 (60)	1 (5)
Dyspnoea	38 (23.8)	11 (6.9)	-	-	-	-
Fatigue	57 (35.6)	14 (8.8)	-	-	4 (20)	1 (5)
Decreased appetite	35 (22)	2 (1.3)	35 (11.2)	1 (0.3)	5	-
Alanine aminotransferase increased	73 (45.9)	18 (11.5)	153 (48.9)	15 (4.8)	3 (15)	-
Lipase increased	53 (33.3)	18 (11.5)	64 (20.4)	15 (5.1)	-	-
Diarrhoea	27 (16.9)	-	90 (28.8)	2 (0.6)	1 (5)	-
Hypoalbuminemia	126 (78.3)	3 (1.9)	246 (78.6)	28 (8.9)	-	-
Temporary treatment discontinuation due to adverse event(s)	84 (52.5)		165 (52.7)		4 (20)	
Dose reduction due to adverse event(s)	53 (33.1)		113 (36.1)		2 (10)	
	EMA: SUMMARY OF PRODUCT CHARACTERISTICS https://www.ema.europa.eu/en/documents/product-information/tabrecta-epar-product-information_en.pdf		EMA: SUMMARY OF PRODUCT CHARACTERISTICS https://www.ema.europa.eu/en/documents/product-information/tepmetko-epar-product-information_en.pdf		eCRF output 7 August 2025 (uncleaned data). AEs related (possibly, probably, very likely related)	

- DO-2 was well tolerated with only two grade 3 TRAE's (fatigue and creatine increase) were seen.
- Most frequent adverse event was reversible serum creatinine increase.
- 1 transient grade 1 edema; outlier PK profile resulting in 24/7 exposure above the ToT and continuous MET kinase. Reducing dose resulted in recovery and no re-appearance of edema.
- Nausea was controlled with standard anti-emetics.

Tumour Shrinkage or Prolonged Stabel Disease Seen in 100% of Patients with ex14 NSCLC (1-3L) Having No Other Known Resistance Drivers or Mechanisms