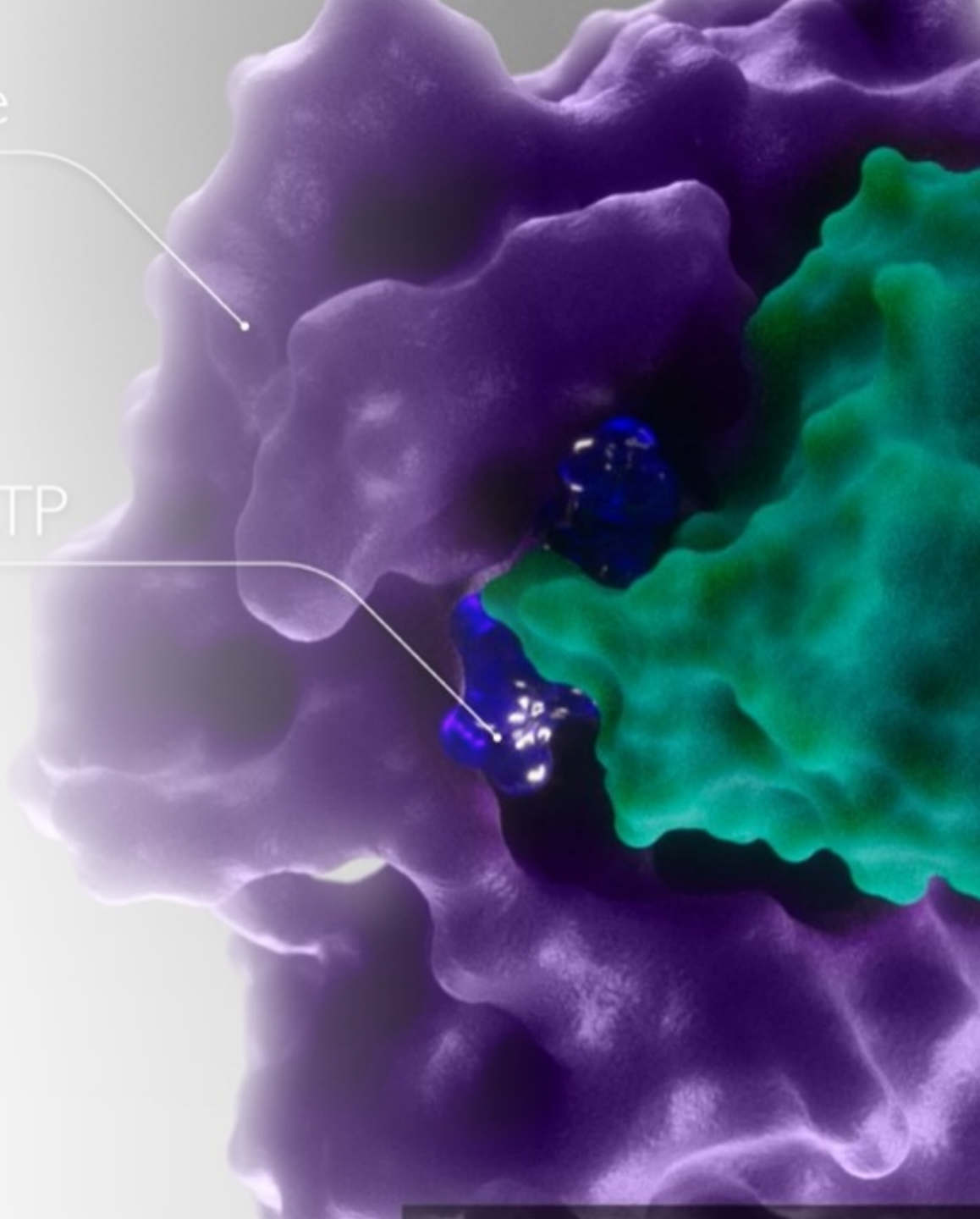
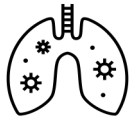
DO-2:
Next generation MET inhibitor

For improved treatment of lung cancer patients



Deuter Oncology

Our value proposition



Potential ‘First in Class’ and ‘Best-in-class’ selective MET kinase inhibitor with very clean safety profile to maintain or extend clinical benefit and allow combination therapy with a range of SOC.

Ongoing Phase 1 study showing clinical benefit and efficacy at low dose levels with minimal adverse events

Strong indicators of clinical benefit: complete clearance of pleural fluid, weight gain, improved breathing. Partial Response and pharmacokinetics at 40mg daily dose are clinically validating DO-2’s value.

Extremely well tolerated with no incidences of drug related peripheral edema or liver enzyme elevations that are commonly seen with competitors;

Company

- Founded in Q4 ‘20 in Belgium by Dr Timothy Perera
  - Dr Perera originated the initial idea for the use of deuteration as a means to modulate the metabolic properties of the parent drug
- Lead compound in-licensed from Janssen Pharmaceutica
- Existing Investors include Newton Biocapital (lead investor), Noshaq and Investsudtech
- Significant know-how on high-efficiency deuteration
- Exclusive global licence from Johnson and Johnson
- IP exclusivity until 2035 – ww rights under parent patent. Novel applications related to dosing regimen submitted 2024

Team

Timothy Perera, PhD.
Founder/CEO

30 y Pharma Experience

OCTIMET CSO/CEO
Global Discovery Leader Lung Disease Area at J&J.
Discovery leader/project champion for 4 clinical stage agents including approved FGFR inhibitor Balversa (erdafitinib)

Els Hubloux
CFO

25 y Life Sciences Experience

Corporate and Venture Capital experience including Pronota, Capricorn Venture Partners, QBIC Venture Partners, Newton Biocapital Venture Partners. Executive roles included CFO, VC fund partner positions.
Experienced board member held various board positions in medtech and biotech companies.

Prof Jaap Verweij
CMO

35 y Clinical Development

Prof Emeritus Erasmus Medical Oncology
Managing Director at The Cancer Drug Development Forum (CDDF)

Alfredo Zurlo
Medical Director

25 y Medical Affairs + Clinical Development

International Medical leader at F. Hoffmann La Roche, responsible for the International launch of Avastin (bevacizumab).
Experienced board member held various CMO positions in biotech companies.

Florence Wastelin M.Sc. MBA.
Clinical Operations

20 y at GSK Biologicals

Leading teams across global projects and leading Clinical Operations department for the development of immunotherapeutics against cancer.

Desiree Kanters
Clinical Operations

24 y Clinical operations

Working within the pharmaceutical, biotech, CRO and consultancy sectors. Early to late-stage clinical programs in roles as Project Manager, Global Trial Lead, Clinical Operations Lead, Head of Clinical Operations and COO.

Hilde Windels MBA.
Corporate Development

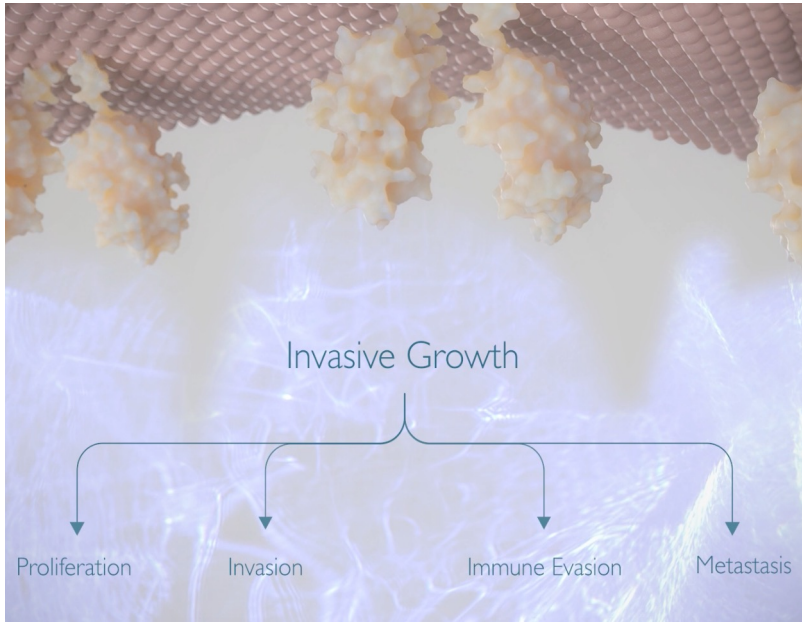
25 y Biotech Experience

Including Devgen, Biocartis and med. and small size biotech companies. Executive roles included CFO, co-CEO and CEO positions.
Board member in 4 public and 1 private company.

Additional support from external partners in targeted outsourced activities as required.

The opportunity

MET, a clinically validated drug target but tolerability remains an issuse



- MET is expressed in normal tissues including vascular endothelial cells
- MET dysregulation is associated with a poor prognosis in a range of cancers
- Clinical activity proven for class
  - Only in 2nd line (in EU) patients with non-small cell lung cancer (NSCLC) harbouring exon14 skipping (METex14) mutations.

Oncogenic driver when wild type receptor is overexpressed due to
- MET amplification
- MET mutation (ex 14 skipping)

~2 to 5 % of advanced NSCLC

- Yet, significant toxicities are seen
  - high daily doses (500-800mg) frequently leading to dose interruptions and reductions.
  - impacting Quality of Life and overall clinical benefit.
- Well tolerated MET inhibitor remains an unmet medical need

Large market potential

- Current MET inhibitors only approved in the METex14 skip mutation positive setting (~3% of NSCLC)
  - Restricted to 2nd line in EU
  - Poor market penetration due to difficult to adverse event profiles that are difficult to manage
- Much larger currently 'unmet medical needs' await a well tolerated MET inhibitor
  - Monotherapy in MET mutant settings
    - MET amplified NSCLC, gastric cancer, ovarian cancer
    - MET amplification/fusions in glioblastomas
    - MET amplification in gastroesophageal cancers
  - Combination settings
    - Intrinsic/acquired resistance to immune checkpoint inhibitors in a range of cancers
    - Acquired resistance to EGFR, kras, Alk, Ros… inhibitors in NSCLC
    - Acquired resistance to EGFR inhibitors in colon and head & neck cancers…

The Market Need

Peripheral edema and liver toxicity frequently observed with approved agents: **not observed with DO-2 in phase I**

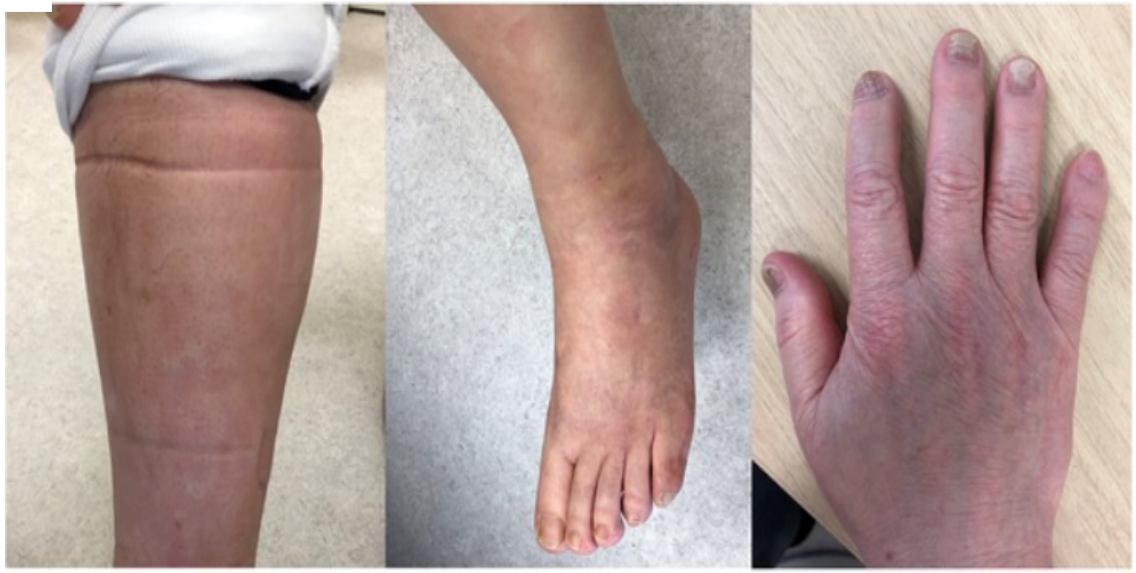


Figure - available from: Thoracic Cancer

Peripheral edema

- 67% of tepotinib[1] and 51% of capmatinib[2] treated patients endure some degree of edema
- Median time to onset of edema 9 weeks[3]
- Peripheral edema; observed in the pre-clinical tox study[4] with tepotinib
- NOT observed with DO-2 (clinical or pre-clinical)

Liver enzyme elevations

- 48% of tepotinib[3] and 46% of capamatinib[2] treated patients
- Liver toxicity; observed in the pre-clinical tox study[4] with tepotinib and capmatinib[6].
- NOT observed with DO-2 (clinical or pre-clinical)

- Tox profile of approved agents considered comparable to SOC (Chemo/Immunotherapy)
- Not reimbursed in many countries
- Not prescribed by some treating oncologists

1 Number of patients : 313 (cohorts A+C) from registration trial VISION (JAMA Oncol. 2023;9(9):1260-1266,doi:10.1001/jamaoncol.2023.1962)
2 Number of patients : 364 (all cohorts) from registration trial GEOMETRY (N Engl J Med 2020;383:944-957, DOI: 10.1056/NEJMoa2002787)
3 https://ec.europa.eu/health/documents/community-register/2022/20220216154592/anx_154592_en.pdf
4 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214096Orig1s000MultidisciplineR.pdf
5 https://ec.europa.eu/health/documents/community-register/2022/20220620155859/anx_155859_en.pdf
6 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213591Orig1s000MultidisciplineR.pdf

Tepotinib can cause intolerable adverse events

eTable 7. Tepotinib safety profile in Cohorts A+C.

AE, n (%)	Overall (N=313)	
	All cause AEs	Treatment-related AEs
Any AE	310 (99.0)	287 (91.7)
Serious AEs	159 (50.8)	49 (15.7)
Grade ≥3 AEs	203 (64.9)	109 (34.8)
Grade ≥4 AEs	57 (18.2)	12 (3.8)
AEs leading to dose reduction	113 (36.1)	105 (33.5)
AEs leading to treatment interruption	165 (52.7)	135 (43.1)
AEs leading to permanent discontinuation	78 (24.9)	46 (14.7)
AEs leading to death*	41 (13.1)	3 (1.0)
Treatment-related AEs occurring in ≥10% of patients, n (%)	**Any grade**	**Grade ≥3**
Peripheral edema	210 (67.1)	35 (11.2)
Nausea	73 (23.3)	2 (0.6)
Diarrhea	70 (22.4)	1 (0.3)
Hypoalbuminemia	74 (23.6)	11 (3.5)
Blood creatinine increase	69 (22.0)	3 (1.0)
Decreased appetite	35 (11.2)	1 (0.3)
Alanine transaminase increase	44 (14.1)	7 (2.2)

*Of the three patients with treatment-related AEs leading to death, two patients were already detailed in Le X et al. *Clin Cancer Res*. 2022;28(6):1117-1126, and the third patient had progressive disease or a lung cancer-related condition leading to multiple organ failure, which was considered treatment-related due to a missing causality report.

Abbreviations: AE, adverse event.

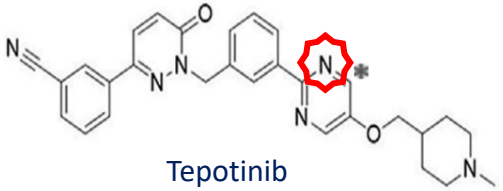
High number of dose reductions or treatment discontinuations

- Treatment-related AEs (TRAEs) occurred in **287 out of 313 patients (91.7%)**, and were **grade 3 or higher in 109 (34.8%)**
  - → Dose reduction 105 (36.1%)
  - → Discontinuation 46 (24.9%)
- Peripheral edema 210 (67.1%)
  - 11.2% experiencing grade 3 or higher peripheral edema.
- Other TRAEs (20%) mostly grades 1 to 2 included
  - hypoalbuminemia 74 patients
  - nausea 73 patients
  - diarrhea 70 patients
  - blood creatinine level increase 69

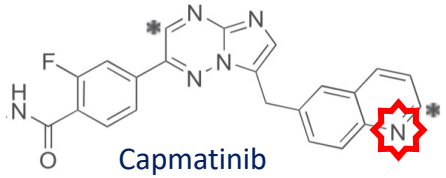
Mazieres et al JAMA Oncol. doi:10.1001/jamaoncol.2023.1962 Published online June 4, 2023.

The solution

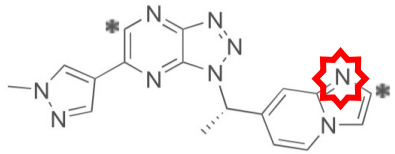
Metabolism of chemical scaffold of selective Type 1B MET kinase inhibitors lead to adverse events



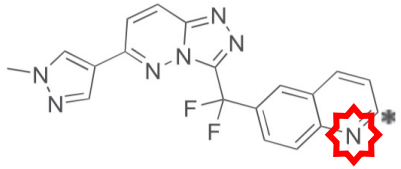
Tepotinib
Approved



Capmatinib
Approved



Savolitinib
Approved



JNJ-38877605 (DO-0)
Terminated

Nitrogen (⬡) => critical for binding to MET

Aldehyde Oxidase 1 replaces the Hydrogen* by a bulky Oxygen which prevents binding to intended target

- Reducing exposure to active parent drug
- Requiring higher daily doses

Most abundant circulating metabolite(s) of parent drug with no/negligible pharmacological activity for:

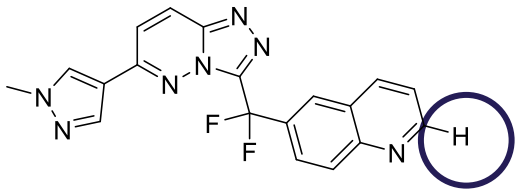
- Capmatinib[1.] ~ 50% inactive metabolite(s)
- Tepotinib[2.] ~ 65% inactive metabolite(s)
- Savolitinib[3.] ~ 88% inactive metabolite(s)
- DO-2 ~ 10% inactive metabolite

1) Glaenzel et al, Drug Metab Dispos 48:873–885, October 2020 : 2) Xiong et al CPT Pharmacometrics Syst. Pharmacol. 2021;10:428 : 3) Miah et al, Clin Pharmacol Drug Dev. 2023 Apr;12(4):424-435

Hypothesis: Deuteration, a small chemical change will make a big impact on parent drug exposure

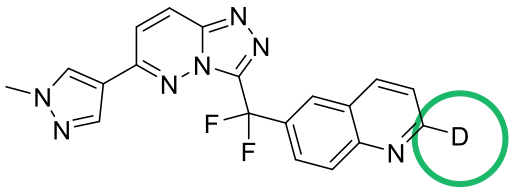
- Deuterated drug: a small molecule in which one or more of the **hydrogen atoms are replaced by deuterium**.
  - As deuterium and hydrogen* have nearly the same physical properties, a deuterium substitution is one of the smallest structural changes that can be made to a molecule.

Non-deuterated parent JNJ-38877605



MW:377.4 Daltons

Deuterated analogue of JNJ-38877605



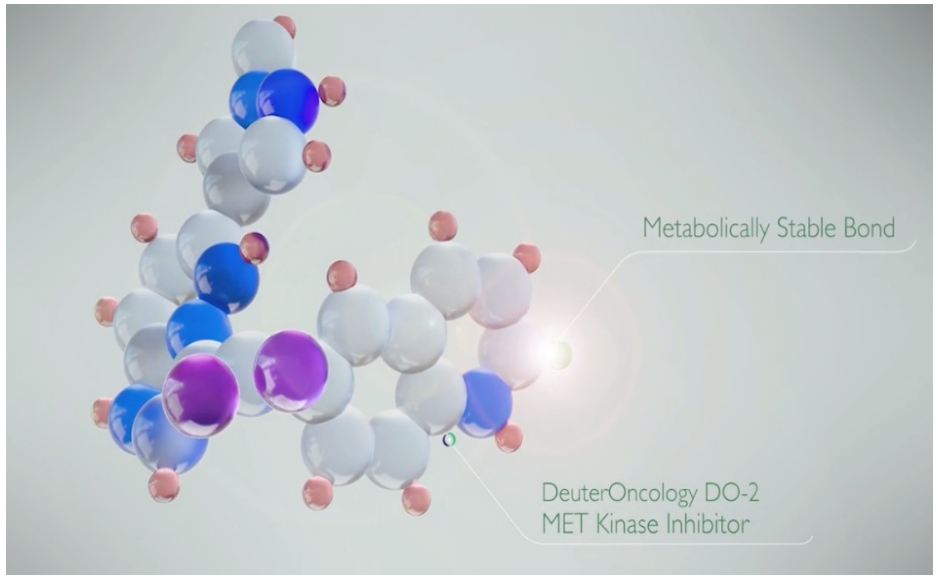
MW:378.4 Daltons

- 'Deuterium-carbon' bonds are 6 to 10 times more stable than the corresponding 'hydrogen-carbon' bonds.
  - More difficult to break resulting in higher active parent drug levels

* Hydrogen consists of 1 electron and one proton
Deuterium, a naturally-occurring, stable, non-radioactive isotope of hydrogen, consists of 1 electron, 1 proton and a neutron

DO-2, a re-engineered MET Kinase inhibitor addressing deficiencies of current agents…

…by replacing a critical hydrogen with a deuterium atom to obtain a stable deuterium-carbon bond.



- Shows increased activity
- High oral bioavailability
- Extends the efficacious plasma exposure profile
- Considerably lower toxicity
- Targets MET ex 14 skipping and MET amplification
- High level deuteration (99%+)

Mechanistic basis for lack of peripheral edema

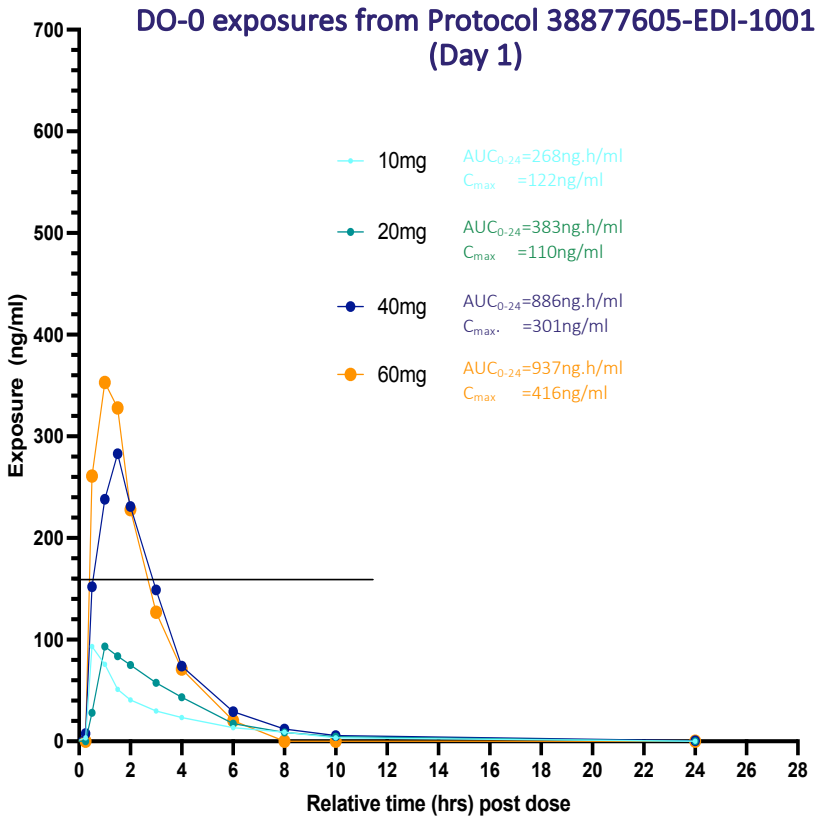
- The HGF/MET pathway contributes to the dynamic control of blood vessel tone and helps maintain vascular homeostasis by
  - promoting NO production
  - maintaining endothelial integrity
  - supporting angiogenesis
- 24/7 inhibition of MET will directly impact these physiological functions including barrier function
  - Peripheral vasculature
  - Blood Brain Barrier
  - High Endothelial Venule
- DO-2 has ‘fast on’ and ‘fast off’ binding kinetics to MET under physiological conditions
- Dosing optimised to achieve required Pharmacokinetic profile to achieve selective, deep cyclic inhibition of target for ~10hrs/day with ~14 hrs ‘drug holiday’ for physiological effects

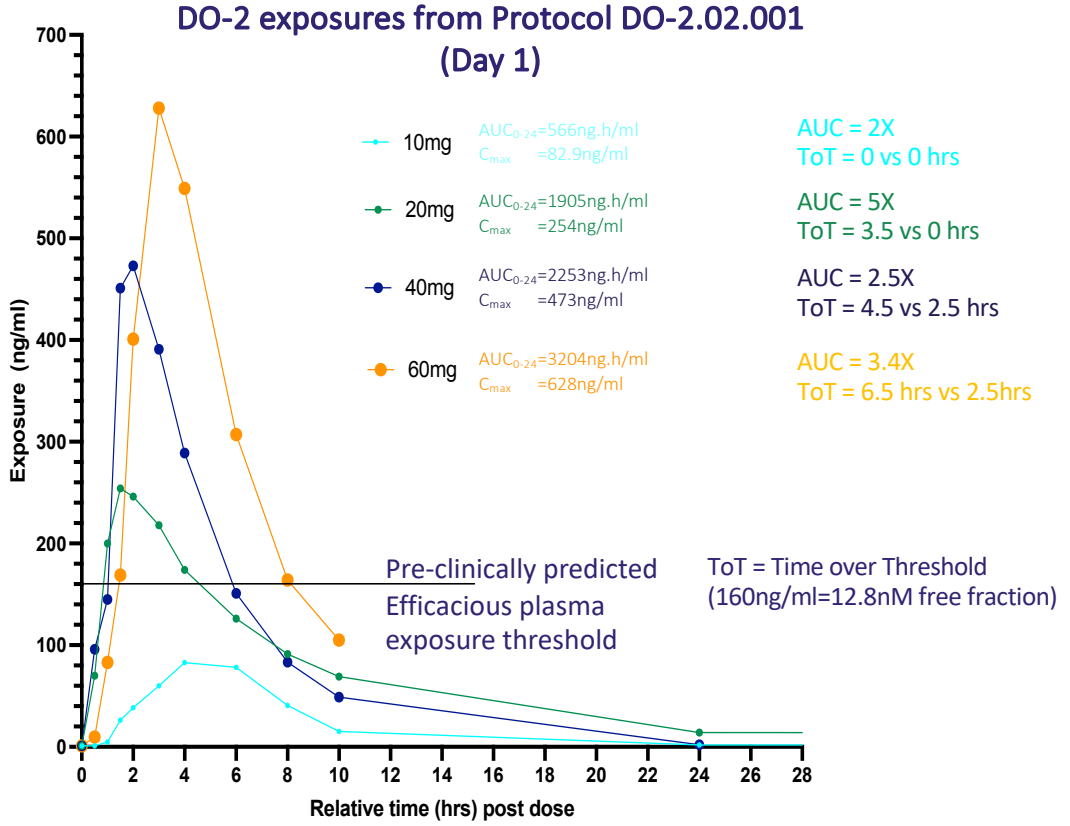
Bussolino F, Di Renzo MF, Ziche M, Bocchietto E, Olivero M, Naldini L, Gaudino G, Tamagnone L, Coffer A, Comoglio PM. Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell motility and growth. J Cell Biol. 1992 Nov;119(3):629-41. doi: 10.1083/jcb.119.3.629. PMID: 1383237; PMCID: PMC2289675.
Yamada N, Nakagawa S, Horai S, Tanaka K, Deli MA, Yatsuhashi H, Niwa M. Hepatocyte growth factor enhances the barrier function in primary cultures of rat brain microvascular endothelial cells. Microvasc Res. 2014 Mar;92:41-9. doi: 10.1016/j.mvr.2013.12.004. Epub 2013 Dec 23. PMID: 24370951.

Clinical Data

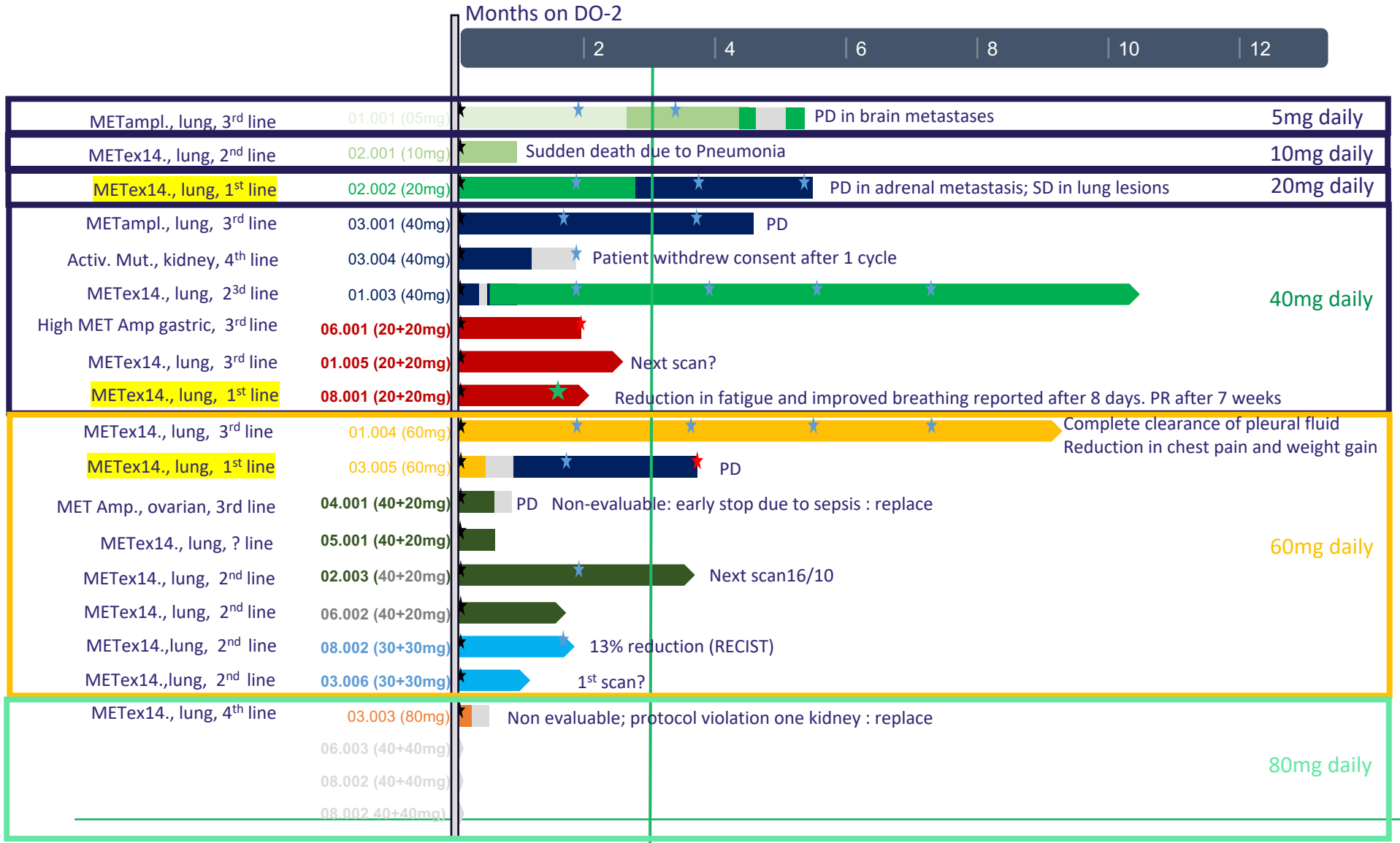
Clinical validation: Significantly improve active (parent) drug exposures

Clinical exposures of deuterated version (DO-2) are ~2.5 to 5-fold higher than with the non-deuterated version (JNJ-38877605/DO-0). DO-2 maintains efficacious levels (ToT) for longer, achieving target inhibition levels.





Partial Response, prolonged Stable Disease and clinical benefit at low dose levels with minimal adverse events



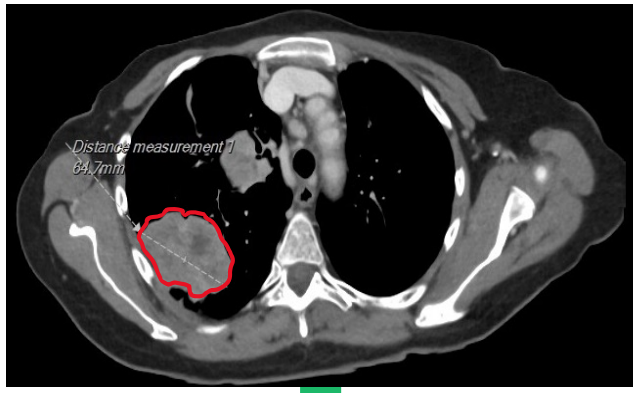
- 18 patients dosed
- 2 non evaluable
- Three 1st line patients enrolled
  - 1 PR +2SD >12 weeks
  - 100% DCR

Data 15th Oct 2024

>12 weeks Stable Disease (SD) = Disease Control in NSCLC

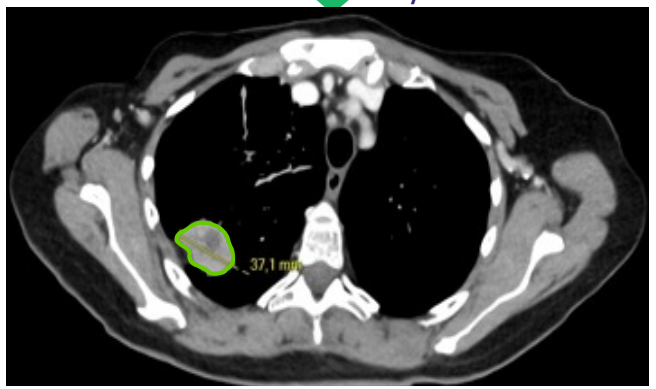
Partial Response seen after 7 weeks on 20+20mg (08.001)

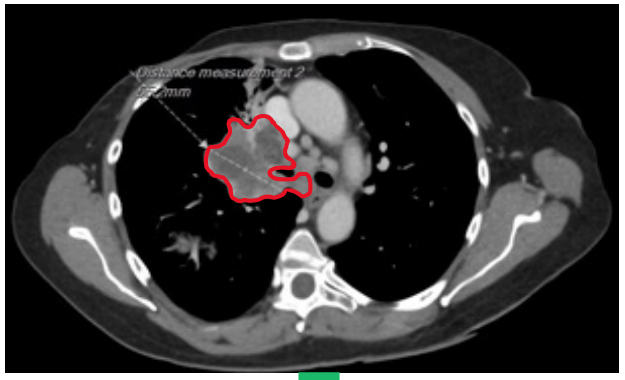
Screening



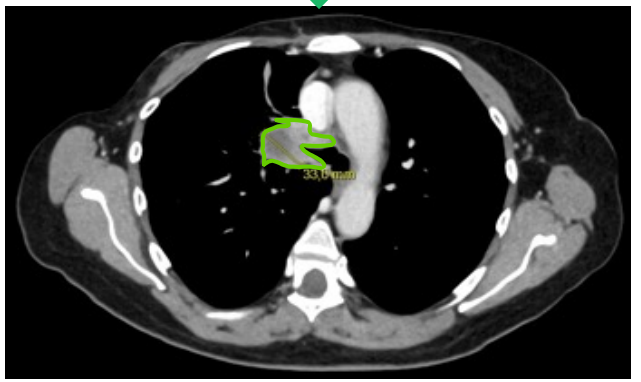
39/65 = -40%

C2D22





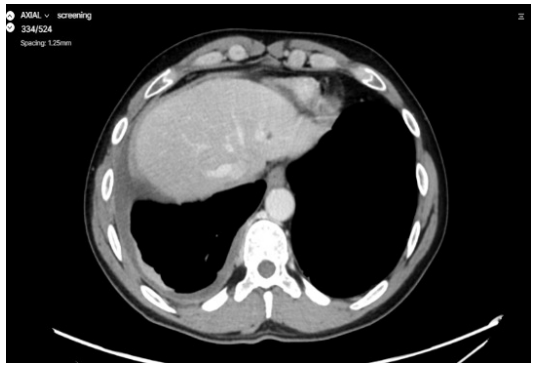
34/55 = -36.2%



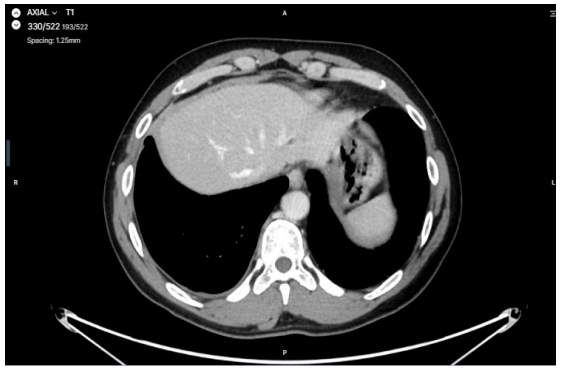
"…..quality of life is improved impressively since start of treatment"

Complete resolution of pleural effusion - Patient 01-004 at 60mg OD

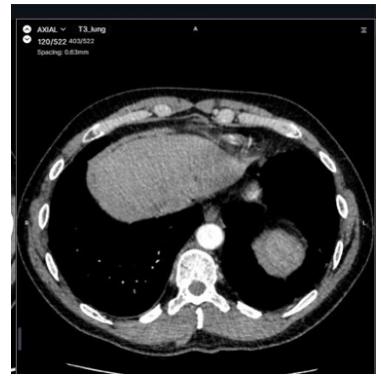
Screening



C1D22

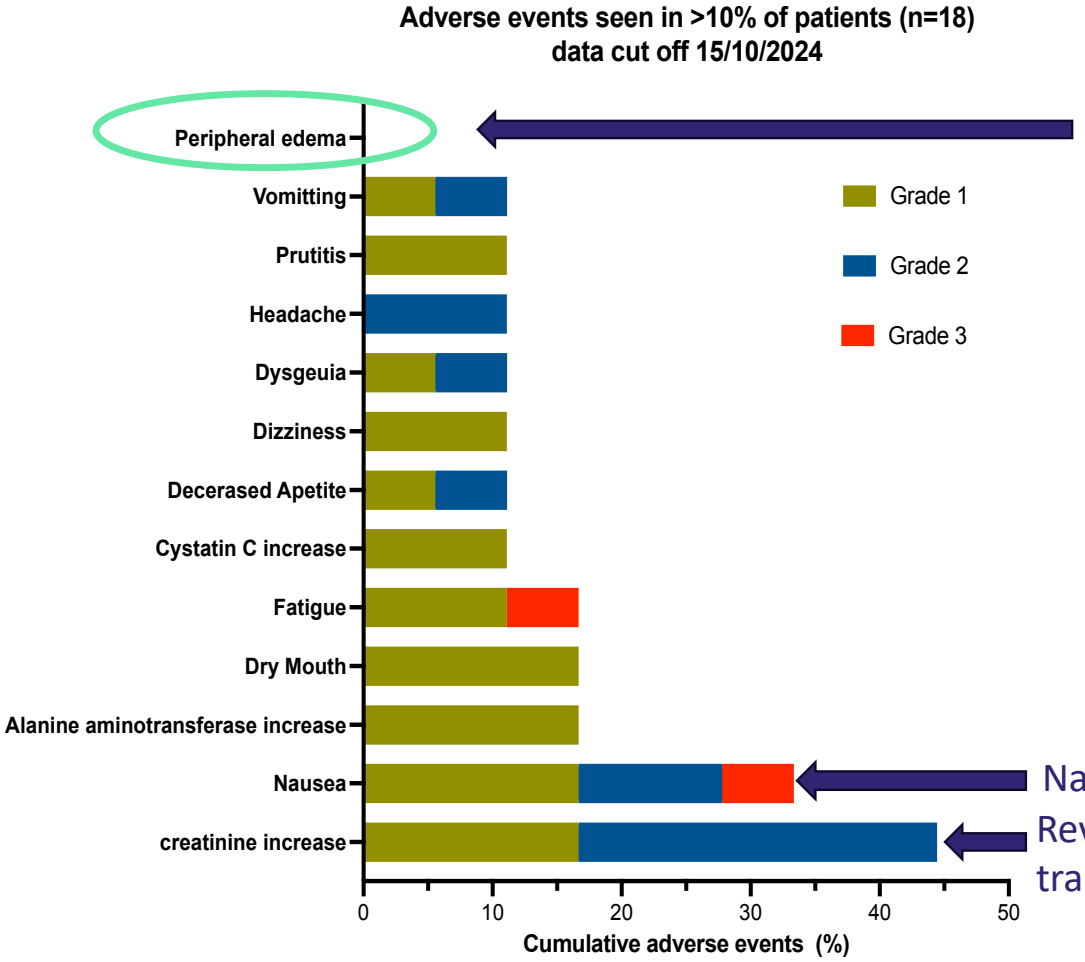


C6D1



- Reduction in chest pain reported at day 8
- Complete absence of chest pain after 2 cycles
- Pleural effusion **completely resolved at C6D1**
- Continuing on treatment for >270 days

Excellent safety profile thus far with no peripheral edema



No evidence of ANY Peripheral edema that is seen in > 50% of patients on tepotinib

Nausea controlled with standars anti-emetics

Reversible creatinine increase expected benign transporter effect due to known OCT-2 inhibition by DO-2

Next steps

Clinical Development Plan

- Phase I
  - Fully funded

- Phase II registrational intent study + start combination studies
  - Financing need: EUR 25 – 50 Mio
  - Potential study cohorts:
    - 1st line exon 14 skipping NSCLC patients
    - 2nd/3rd line exon 14 skipping NSCLC patients
  - Initial combination indication
    - NSCLC combination with EGFRi

Wrap Up

- **Promising Phase I clinical data**
- 1 Partial Response (RECIST) at 40mg daily dose (after 7 weeks)
- 2 patients with prolonged Stable Disease (>8 months and ongoing: 1 at 20mg and 1 at 60mg)
  - Complete clearance of pleural effusions and volume reductions in 'non measurable' lesions (non RECIST)
  - Weight gain, alleviation of pain, reduction in fatigue, feeling 'better and better'
  - No peripheral edema or liver enzyme elevations seen
    - Mechanistic basis for lack of edema now understood
- **Improvement over competitive drugs observed in (pre)-clinical studies with convincing data.**
  - **Superiority** of DO-2 over main competitors at much lower doses **that translates into the clinic**.
  - Large therapeutic window
  - Similar potency in MET amp and MET ex14 skip setting (minimum effective dose <0.5mg/kg)
  - Brain penetrant $K_{P,uu}$ of 0.3
- **Compound and drug product manufacture optimized with long shelf life.**
- **Significant market opportunity for First in Class (1st line EU) and Best in Class (2nd/3rd line) as single agent a well as multiple combination therapy settings**

Dr Timothy Perera

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