Safety and efficacy of first-in-class, YAP/TEAD inhibitor, VT3989 in refractory pleural and non-pleural mesothelioma: A Phase I/II study

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Declaration of Interests

Timothy A. Yap, MD, PhD

Disclosures:

- **Employment:** University of Texas MD Anderson Cancer Center; where I am Vice President, Head of Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in DNA damage response (DDR) and other inhibitors (IACS30380/ ART0380 was licensed to Artios)
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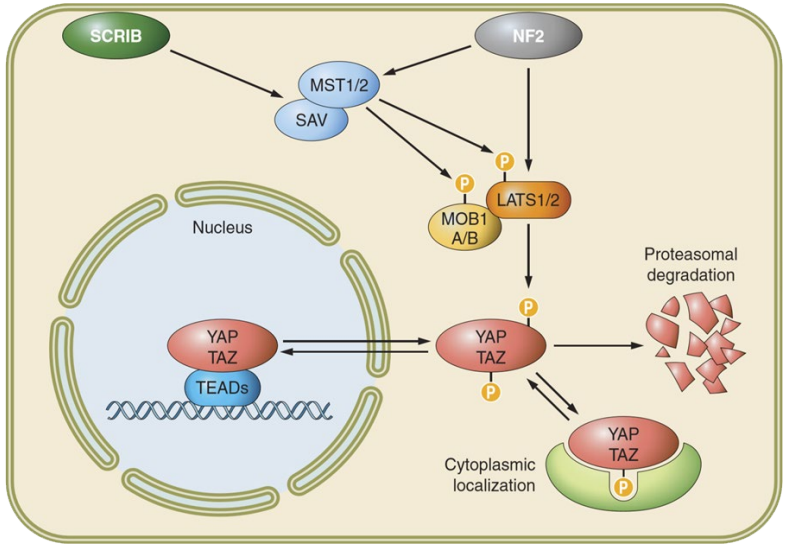
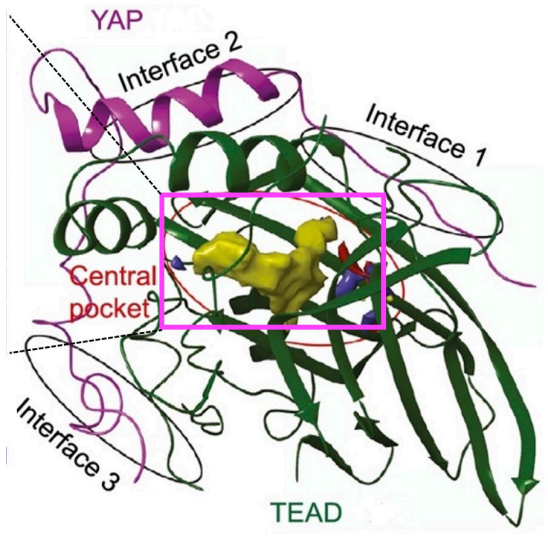
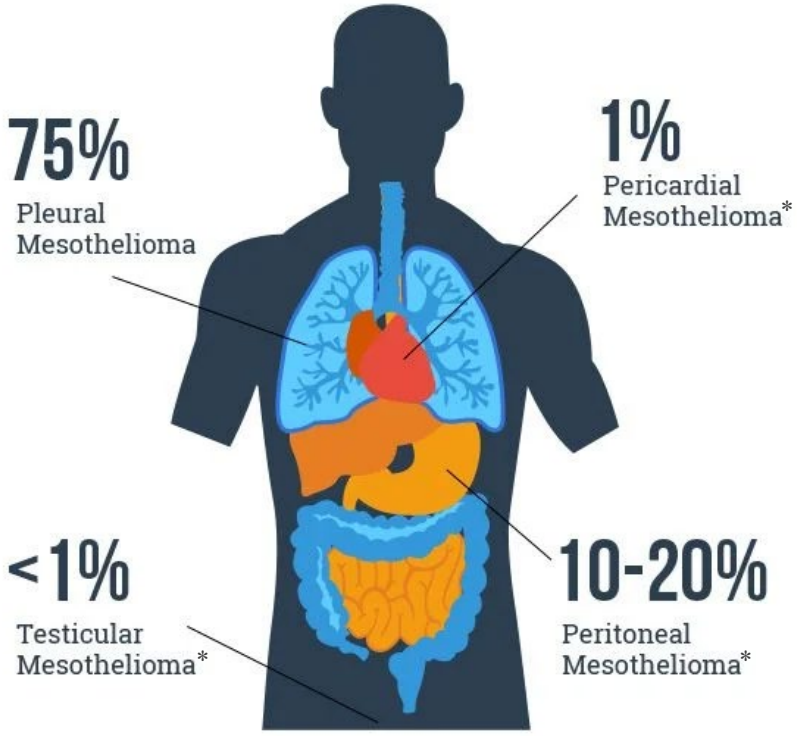
VT3989: First-In-Class TEAD inhibitor





- Hippo signaling inhibits YAP and TAZ by blocking nuclear translocation and interaction with TEAD in the nucleus
- NF2 Mutation or loss of Merlin (gene product of NF2) leads to Hippo dysregulation
  - Common in mesothelioma (~70%); molecular patient selection is not required
- VT3989 is a small molecule auto-palmitoylation inhibitor of TEAD
  - Palmitoylation of a conserved cysteine in the YAP-binding domain is required for YAP-TEAD interaction
  - VT3989 occupies the palmitate pocket blocking the YAP-TEAD interaction and inhibiting transcriptional activity

Unmet Need for Targeted Mesothelioma Therapies



*NPM: Non-pleural mesothelioma

- **5-year survival:**
  - 10% for pleural mesothelioma (PM)
  - 20% for peritoneal mesothelioma
- **Median OS in PM after 2L therapy is only 6-8 months**
- **No targeted treatments approved**
- **Limited systemic treatment options**
  - Platinum/Pemetrexed, or Ipilimumab/Nivolumab, or Pembrolizumab/Platinum/Pemetrexed
  - Most commonly used chemo for 3rd line (Vinorelbine or Gemcitabine) is IV – poor activity with significant toxicity

VT3989-001: Ph1/2 Study of VT3989 in patients with advanced solid tumors (NCT04665206)

Advanced refractory solid tumors, including pleural/non-pleural mesothelioma

VT3989-001-Part 1
(Dose Escalation, N=85)

3+3 Dose Escalation
Continuous Dose
(25mg to 200mg)

and various intermittent schedules

→ **No MTD** →

VT3989-001-Part 2
(Dose Expansion, N=87)

- **EC-1**: 100 mg daily 2W/2W (NPM/PM), N=27
- **EC-2**: 50mg daily 2 Weeks followed by 100 mg weekly (NPM/PM), N=27

→ **RP2D** →

- **EC-3**: 100 mg daily 2W/2W (NPM), N=17
- **EC-4**: 100 mg daily 2W/2W (Other Solid tumors), N=12
- **EC-5**: 100 mg daily 2W/2W (PM), N=4

Relevant Inclusion Criteria:

- ECOG PS 0-1
- Hgb ≥ 9g/dl, ANC ≥ 1.5K/µL, Platelets ≥ 100K/µL, ALT/AST ≤ 2.5 × ULN, Bilirubin ≤ 1.5 mg/dL, Creatinine ≤ ULN, eGFR ≥ 60 mL/min if creatinine 1–1.5 × ULN, Serum albumin > 2.5 g/dL, UACR ≤ 300 mg/gm
- *NF2* mutation status collected but not required for enrollment

Primary Endpoints:

- Safety and Tolerability
- Maximum Tolerated Dose (MTD) & Recommended Phase 2 Dose (RP2D)

Secondary Endpoints:

- Antitumor activity
- Pharmacokinetics
- Time to response
- Time match PK and ECG

Exploratory Endpoints:

- Hippo-YAP signaling in sequential tumor biopsies
- ctDNA changes
- YAP and Merlin expression by IHC

■ at RP2D

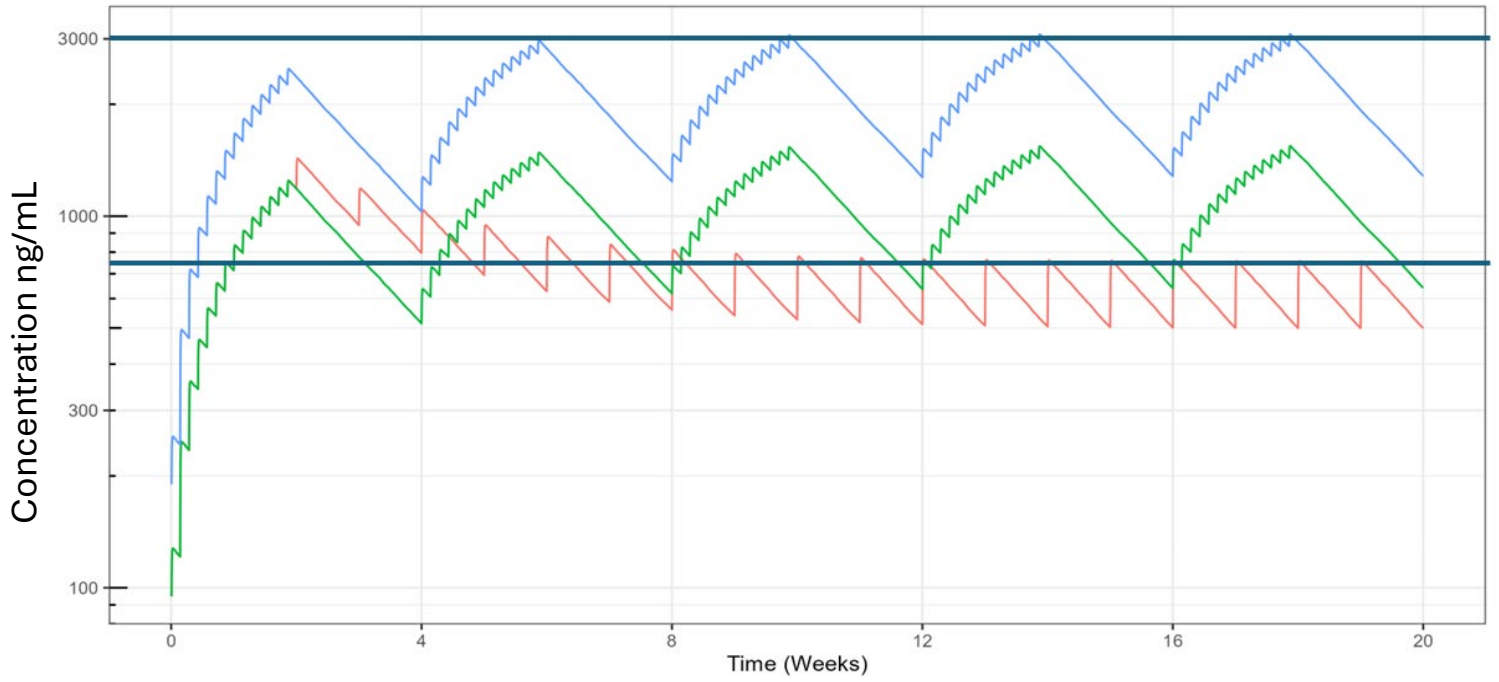
Data as of 20-March-2025

VT3989 Dosing and Exposure Modeling

100 mg QD 2 Weeks on/2 Weeks off (100 mg QD 2W/2W) selected as RP2D

- VT3989 half life: ~ 9 Days
- Intermittent dosing at 100 mg QD 2W/2W provides optimal therapeutic exposure
- 100 and 50 mg QD 2W/2W dose regimens demonstrated clinically meaningful activity
  - 50 mg QD 2W/2W serves as a dose reduction option

Simulated Plasma Concentration – Time Profiles for VT3989 under three Intermittent Dosing Regimens



Blue lines (750-3000 ng/mL) represent the approximate therapeutic exposure range estimated from exposure-response analyses and associated with anti-tumor efficacy.

Baseline Demographics and Characteristics

Characteristics	(N=172)
Age	
Median age in years (range)	65.0 (21–88)
Gender	
Female (%)	66 (38.4)
Male (%)	106 (61.6)
Race	
White (%)	144 (83.7)
Black (%)	8 (4.7)
Asian (%)	3 (1.7)
American Indian (%)	1 (0.6)
Other (%)	16 (9.3)
Ethnicity	
Hispanic (%)	12 (7.0)
ECOG Performance Status	
0 (%)	36 (20.9)
1 (%)	136 (79.1)

Characteristics	(N=172)
Tumor Types, n (%)	
Mesothelioma - Pleural	91 (52.9)
Epithelioid	77 (44.8)
Sarcomatoid*	14 (8.1)
Mesothelioma – Non-Pleural	44 (25.6)
Epithelioid	44 (25.6)
Sarcomatoid*	0 (0.0)
Other Solid Tumors	37 (21.5)
EHE	9 (5.2)
Meningioma	9 (5.2)
Other	19 (11.0)
Molecular Profile, n (%)	
NF2 Mutation	54 (31.4)
NF2 Mutation Undetected	42 (24.4)
Unknown or Not Performed	76 (44.2)
Prior Therapy	
Median (Range)	3 (0–8)
Prior Systemic Therapy (%)	138 (80.2)
Prior Platinum Therapy (%)	125 (72.7)
Prior Immunotherapy (%)	123 (71.5)

*includes biphasics: ≥50% sarcomatoid component

VT3989 is Safe and Well tolerated

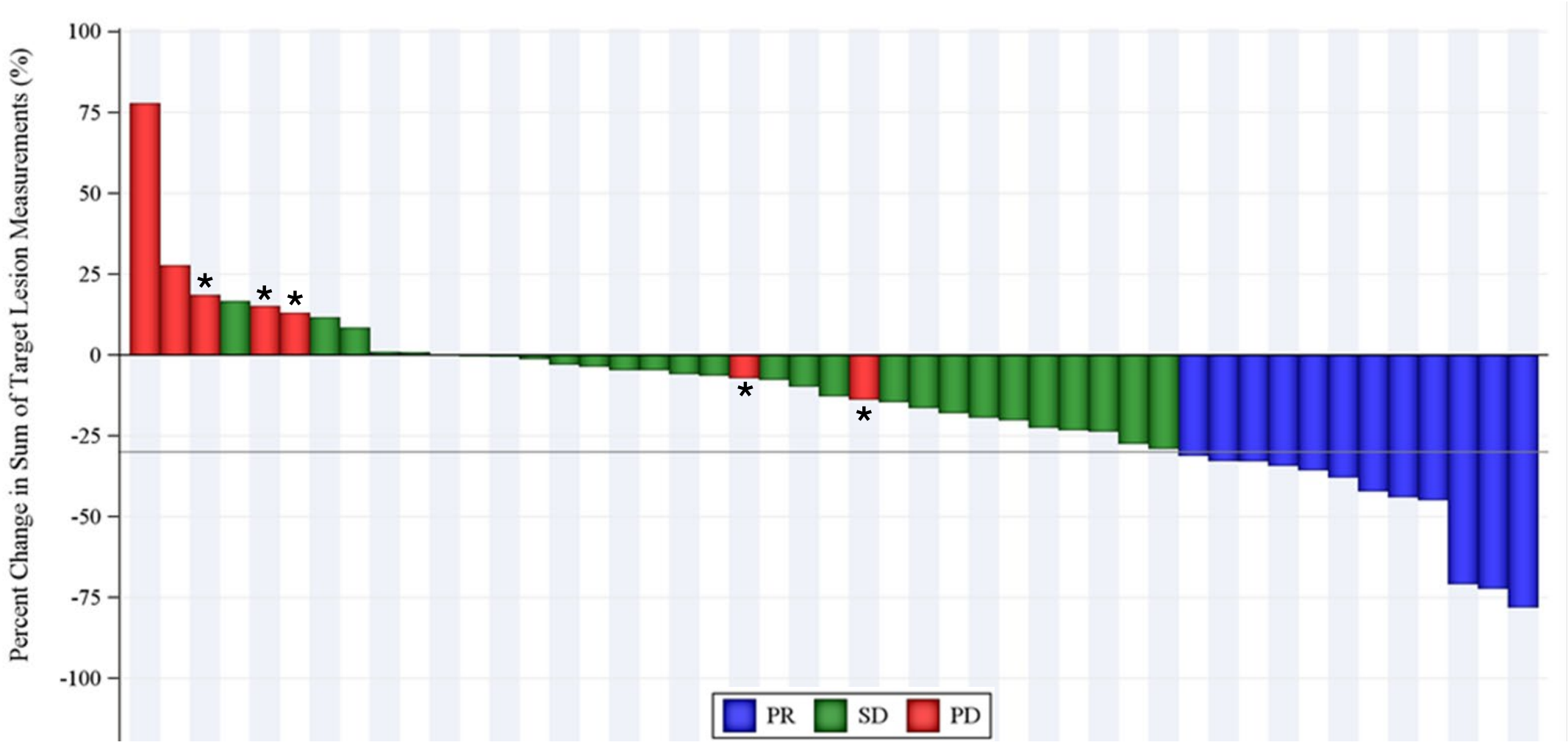
TEAEs in ≥10% of Participants (All Grades, Grades ≥3; N=172)

- Most reported events are mild or moderate in severity
- Treatment related SAEs occurred infrequently, n=10 (5.8%)
- The most common treatment related AEs were low grade fatigue, proteinuria and peripheral edema
- Proteinuria is reversible
- No decline in creatinine clearance or serum albumin
- Discontinuation due to AEs: 3.5%

	Total N=172: n (%)			
	TEAEs		TRAEs	
Preferred Term:	Total	Grade 3/4	Total	Grade 3/4
Subjects with any TEAEs / TRAEs	165 (95.9)	62 (36.0)	138 (80.2)	**15 (8.7)**
Fatigue	69 (40.1)	2 (1.2)	34 (19.8)	**1 (0.6)**
UACR increased	56 (32.6)	3 (1.7)	54 (31.4)	**3 (1.7)**
Nausea	49 (28.5)	0 (0.0)	25 (14.5)	**0 (0.0)**
Proteinuria	49 (28.5)	0 (0.0)	48 (27.9)	**0 (0.0)**
Peripheral oedema	48 (27.9)	1 (0.6)	40 (23.3)	**0 (0.0)**
Dyspnoea	45 (26.2)	12 (7.0)	4 (2.3)	**2 (1.2)**
Anaemia	39 (22.7)	8 (4.7)	11 (6.4)	**0 (0.0)**
Constipation	36 (20.9)	0 (0.0)	6 (3.5)	**0 (0.0)**
Decreased appetite	35 (20.3)	0 (0.0)	8 (4.7)	**0 (0.0)**
Cough	33 (19.2)	0 (0.0)	3 (1.7)	**0 (0.0)**
Dizziness	31 (18.0)	0 (0.0)	6 (3.5)	**0 (0.0)**
Hyponatraemia	28 (16.3)	2 (1.2)	3 (1.7)	**0 (0.0)**
Arthralgia	27 (15.7)	0 (0.0)	2 (1.2)	**0 (0.0)**
Headache	27 (15.7)	0 (0.0)	3 (1.7)	**0 (0.0)**
Diarrhoea	26 (15.1)	0 (0.0)	6 (3.5)	**0 (0.0)**
Vomiting	25 (14.5)	1 (0.6)	7 (4.1)	**0 (0.0)**
AST increased	24 (14.0)	1 (0.6)	13 (7.6)	**1 (0.6)**
Hypotension	24 (14.0)	3 (1.7)	4 (2.3)	**1 (0.6)**
Periorbital oedema	22 (12.8)	0 (0.0)	20 (11.6)	**0 (0.0)**
Blood creatinine increased	22 (12.8)	0 (0.0)	13 (7.6)	**0 (0.0)**
Pleural effusion	21 (12.2)	4 (2.3)	2 (1.2)	**0 (0.0)**
Abdominal distension	20 (11.6)	0 (0.0)	4 (2.3)	**0 (0.0)**
ALT increased	20 (11.6)	1 (0.6)	12 (7.0)	**1 (0.6)**
Abdominal pain	19 (11.0)	1 (0.6)	1 (0.6)	**0 (0.0)**
Back pain	18 (10.5)	1 (0.6)	0 (0.0)	**0 (0.0)**

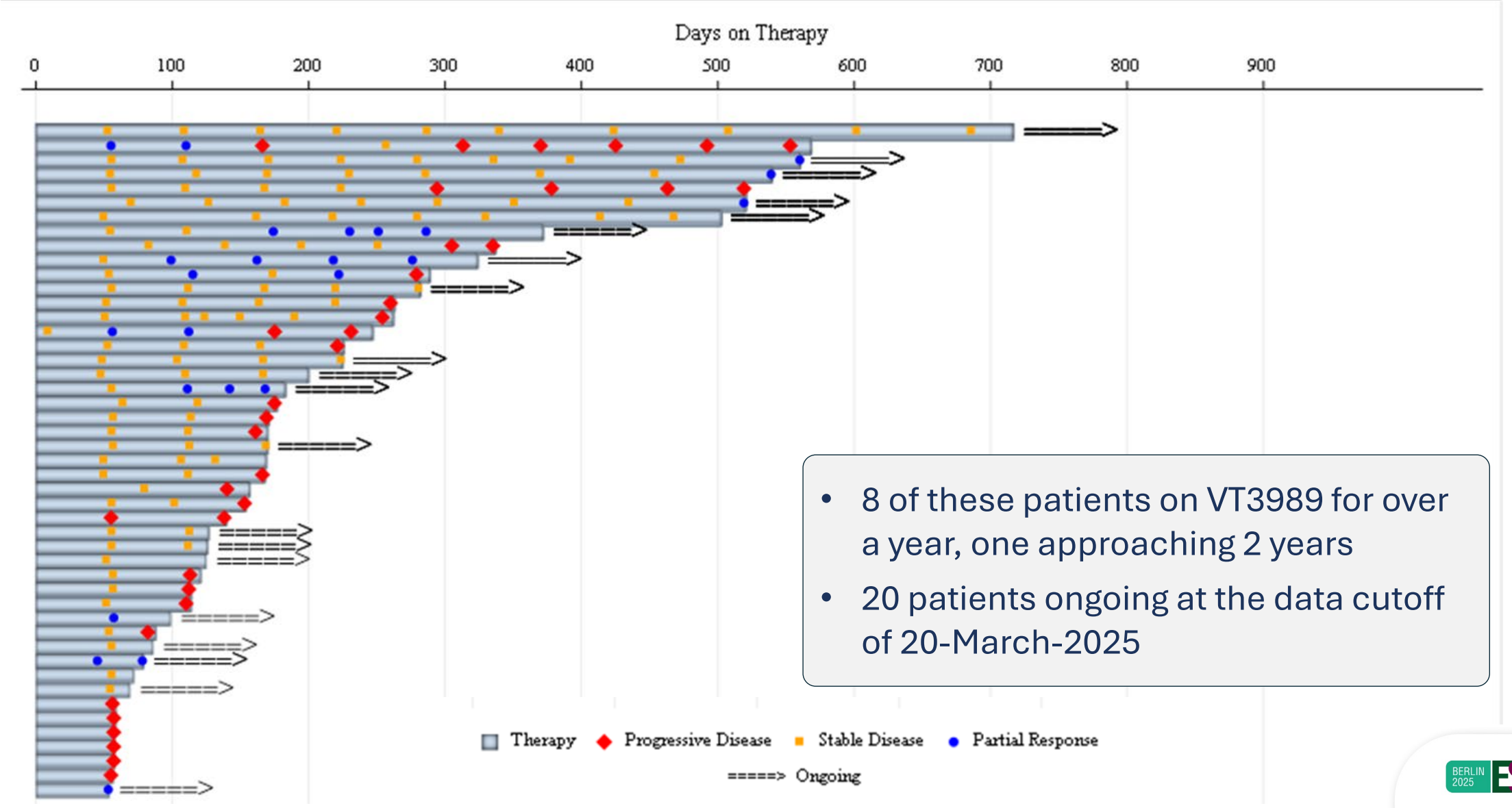
Compelling Efficacy with Broad Tumor Shrinkage

Mesothelioma patients treated at clinically optimized dose (50 or 100 mg 2W/2W, n=47)



* PD due to new lesion or increase in non-target lesion

Durable Clinical Benefit at Clinically Optimized Dose (n=47)



- 8 of these patients on VT3989 for over a year, one approaching 2 years
- 20 patients ongoing at the data cutoff of 20-March-2025

VT3989 has Superior Safety and Efficacy in Mesothelioma Compared to Salvage Chemotherapy

		N=47*	N=22**
Best Response[1]			
Partial Response	n (%)	12 (26)	7 (32)
Stable Disease	n (%)	28 (60)	12 (54)
Progressive Disease	n (%)	7 (15)	3 (14)
Disease Control Rate[2]	n (%)	40 (85)	19 (86)
Clinical Benefit Rate[3]	n (%)	21 (45)	8 (36)
Duration of Response (weeks)[4]	Median	24	NE
	25th, 75th	17.14, NE	23.57, NE
Progression Free Survival (weeks)[4]	Median	25	40
	25th, 75th	16.14, 43.57	24.14, NE
Subjects with Disease Progression	n (%)	25 (53)	6 (27)
Subjects who Died	n (%)	1 (2)	0
Censored Subjects	n (%)	21 (45)	16 (73)

SOC (gemcitabine or vinorelbine)		
ORR	5-8%	
PFS (weeks)	15	
Safety Profile	G3/4 neutropenia	(69%)
	Peripheral neuropathy	(25%)
	Injection site reaction	(16%)
	Vomiting	(20%)
	Diarrhea	(17%)

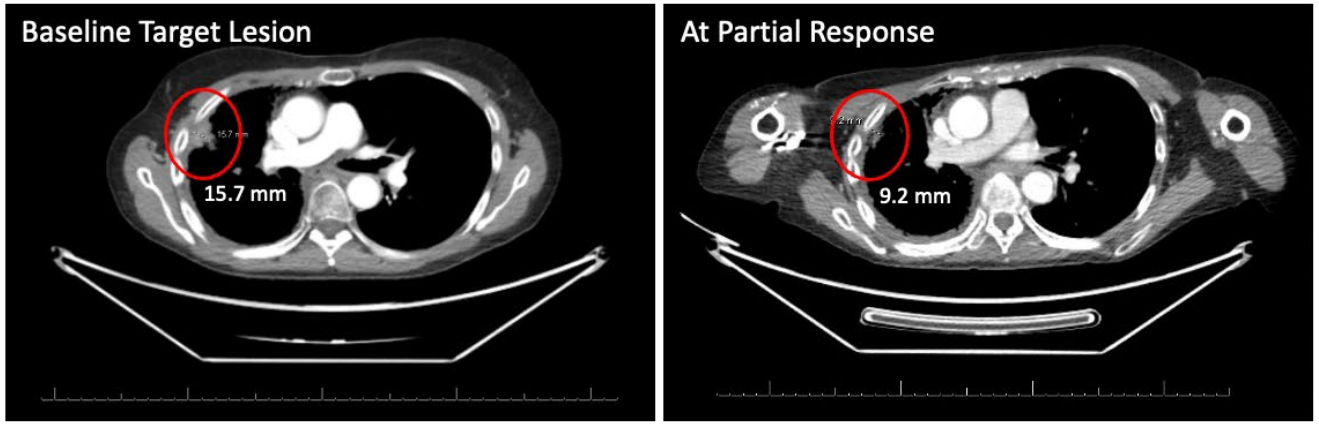
EClinicalMedicine. 2022;48:101432
Lancet Oncol. 2021;22(10):1438-1447
Lancet Oncol. 2017;18(9):1261-1273
Ann Oncol. 2020;31(12):1734-1745
Lancet Oncol. 2018;19(6):799–811
Lancet Oncology. 2022 Apr 1;23(4):540-52
Lung Cancer. 2014 Jun 1;84(3):271-4

*Clinically optimized dose regardless of UACR threshold
**Clinically optimized dose and optimal UACR threshold, all 22 patients previously received IO therapy

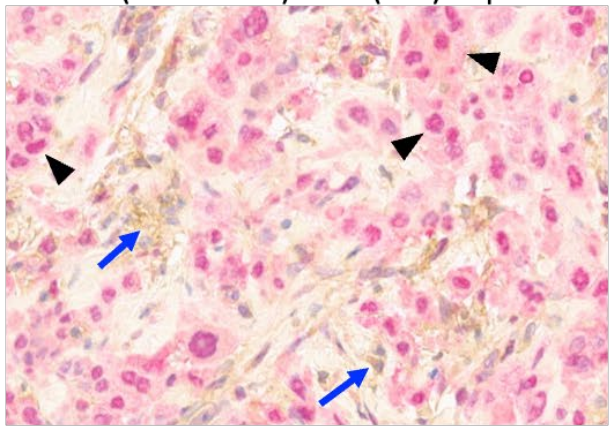
Notes: Duration of response is the duration from the date of response (CR or PR) to the date of progression (PD) via scan or death. Patients who did not respond or die will be censored at the date that the patient was last known to be alive and progression-free (i.e., last scan date). The data cut used for this table is 20March2025. [1]PR and CR do not need to be confirmed. [2]Disease Control Rate = CR + PR + at first disease assessment. [3]Clilnical Benefit Rate = CR+PR+SD lasting ≥ 24 weeks (corresponding to three disease assessments). [4]Based on Kaplan Meir Methods, Disease Progression is via scan or clinical progression. NE: Not Estimable

VT3989 partial response in mesothelioma patients without NF2 mutations show loss of Merlin

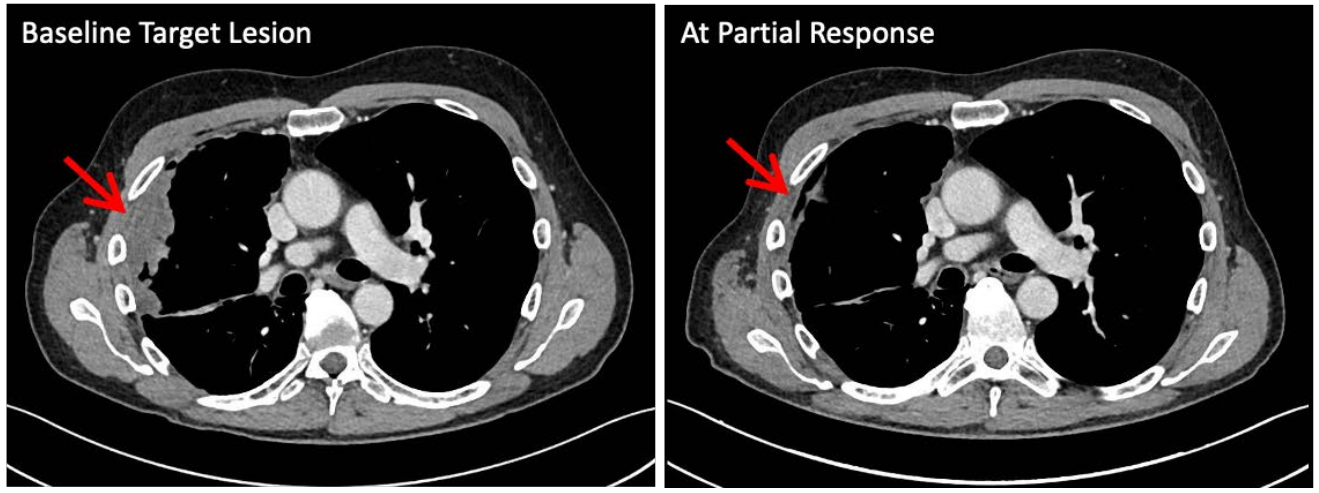
Case 1: Pleural Mesothelioma (No *NF2* mutation detected) PR -43.8%



Merlin (DAB-Brown) - YAP (Red) Duplex IHC



Case 2: Pleural Mesothelioma (No *NF2* mutation detected) PR -69.8%



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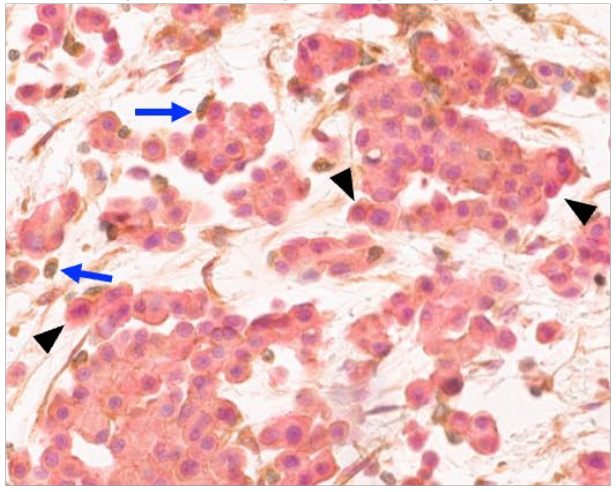

- Black arrowhead: Tumor cells Merlin negative; nuclear YAP positive (Red)
- Blue arrow: Lymphocytes Merlin positive staining (Brown)

Conclusions

VT3989-001:

- Compelling efficacy in pleural and non-pleural refractory mesothelioma
- Favorable safety profile with few ≥ grade 3 TRAEs (N=172)
- Proteinuria is reversible with no decline in creatinine clearance or serum albumin
- Optimal balance of efficacy and safety achieved through intermittent dosing and UACR dose modification threshold
- Results support a registrational 3L Phase 3 study in mesothelioma
- Study data led to FDA Orphan Drug and Fast Track Designations for the treatment of patients with mesothelioma

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Study Teams

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