First-in-class, first-in-human phase 1 trial of VT3989, an inhibitor of Yes-Associated Protein (YAP)/Transcriptional Enhancer Activator Domain (TEAD), in patients with advanced solid tumors enriched for malignant mesothelioma and other tumors with neurofibromatosis 2 (NF2) mutations

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Disclosure Information

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Timothy A. Yap

I have the following financial relationships to disclose:

- **Employment:** University of Texas MD Anderson Cancer Center; where I am Medical Director of the Institute for Applied Cancer Science, which has a commercial interest in DNA damage response (DDR) and other inhibitors (IACS30380/ ART0380 was licensed to Artios)
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- **Stockholder in:** Seagen

Hippo - YAP Pathway

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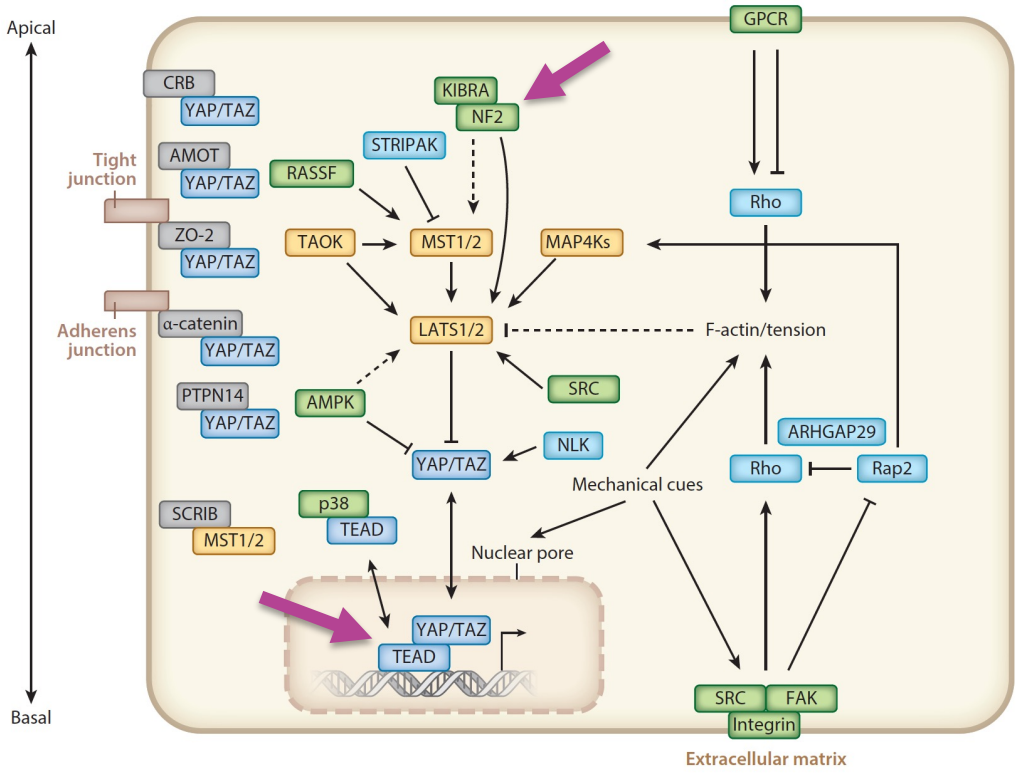

Figure adapted from Ma et al., *Annu Rev Biochem*, 2019

- Hippo signaling regulates transcription factors YAP and TAZ in response to diverse upstream signals.
- When translocated to nucleus, YAP/TAZ interact with DNA-binding TEAD proteins, activating transcription of target genes.
- Dysfunction of Hippo pathway in tumors promotes activation of YAP/TAZ, resulting in uncontrolled proliferation and impaired differentiation.
- *NF2* mutations are one mechanism by which Hippo control of YAP/TAZ is inactivated in tumors and are common in mesothelioma[1].

1. Creaney et al., *Genome Med,* 2022

VT3989 inhibits TEAD-YAP

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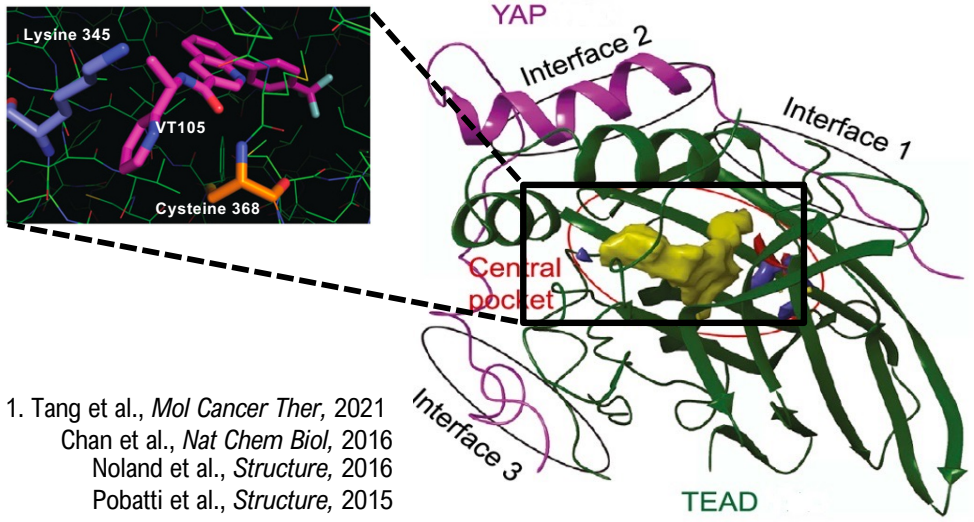
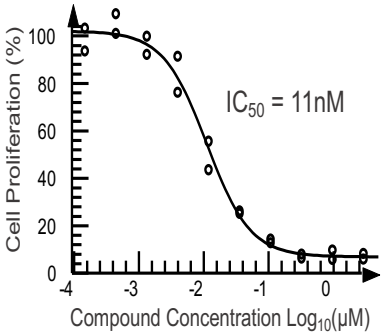
Palmitoylation of a conserved cysteine is required for TEAD interaction with YAP. The palmitate is buried in a central pocket in the YAP-binding domain of TEAD



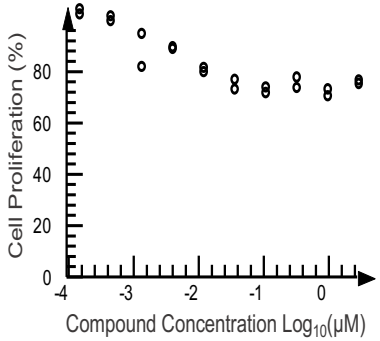
1. Tang et al., *Mol Cancer Ther,* 2021
Chan et al., *Nat Chem Biol,* 2016
Noland et al., *Structure,* 2016
Pobatti et al., *Structure,* 2015

VT3989 occupies the palmitate pocket, inhibiting palmitoylation, and thereby inhibiting transcription function of TEAD-YAP

NCI-H2052
(NF2 homozygous mutant)



NCI-H2452
(NF2 wildtype)



- Mesothelioma cell lines treated with VT3989 show selectivity for NF2 deficiency.
- Activity observed in merlin-negative mesothelioma lines with and without detected *NF2* mutations.
- Active in NF2 deficient mesothelioma xenografts at 3 mg/kg QD oral dosing[1].

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First-in-class First-in-human Phase 1 study of VT3989 in patients with advanced solid tumors

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Dose escalation, 3+3 dose escalation with "back fill" slots

Advanced refractory solid tumors, enriched for malignant pleural mesothelioma and other tumors with *NF2* mutations

→ VT3989 DL1 / VT3989 DL2 / VT3989 DL3 / VT3989 DL4 / VT3989 DL5 → **MTD RP2D**

Dose expansion, 2-stage design

Cohort 1 (n = 10-27)
Mesothelioma patients with or without *NF2* mutations; 100 mg/day 2 weeks on and 2 weeks off, every 4 weeks

Cohort 2 (n = 10-27)
Mesothelioma patients with or without *NF2* mutations 50 mg/day for 15 days then 100 mg/week thereafter

Cohort 3
TBD

Dosing: 3 or 4 week-treatment cycles
Tumor response assessment approximately every 8-9 weeks
Relevant inclusion criteria:

- ECOG PS 0-2
- Hgb ≥ 8 g/dL, ANC ≥ 1.5K/uL, Platelets ≥ 100K/uL, ALT/AST ≤ 2.5 x ULN, Bili ≤ 1.5 mg/dL, Creatinine ≤ ULN, Estimated GFR ≥ 60 mL/min if creatinine 1-1.5 x ULN, Serum albumin > 2.5 g/dL, UACR* ≤ 100 mg/gm

*Eligibility used UPCR ≤ 0.5 mg/mg initially; later updated to UACR ≤ 100 mg/gm

Primary endpoints:

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

Secondary endpoints

- Preliminary antitumor activity in *NF2* mutation solid tumors
- Pharmacokinetics
- Time to response and duration of response
- Time match PK and ECG

Exploratory endpoints

- Hippo-Yap signaling in sequential tumor biopsies
- ctDNA changes
- YAP & Merlin by IHC

UACR: Urine albumin-creatinine ratio

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Baseline Patient Characteristics
Part 1, Cohorts 1-12

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Characteristic	(n=69)
Age	
Median age in years (range)	63.5 (21-83)
Gender	
Female (%)	34 (49)
Male (%)	35 (51)
Race	
White (%)	60 (87)
Black (%)	2 (3)
American Indian (%)	1 (1)
Other (%)	6 (9)
Ethnicity	
Hispanic (%)	7 (10.1)
ECOG Performance Status	
0 (%)	11 (16)
1 (%)	58 (84)

ECOG: Eastern Cooperative Oncology Group; CPI: Immune Checkpoint Inhibitor; VEGF: Vascular Endothelial Growth Factor; NSCLC: Non-small cell lung cancer; EHE: Epithelioid hemangioendothelioma; MPNST: Malignant Peripheral Nerve Sheath Tumor

Characteristic	(n=69)
Tumor Types	
Pleural Mesothelioma	33 (48)
Peritoneal Mesothelioma	8 (12)
Dual Pleural & Peritoneal Mesothelioma	1 (1)
Pericardial Mesothelioma	1 (1)
Meningioma	9 (13)
Other Solid Tumor	17 (23)
Molecular Profile	
NF2 Mutations	37
Somatic	31
Germline	6
NF2 Wildtype	13
Unknown	19
Prior Therapy	
Median (Range)	3 (0-8)
Prior chemotherapy (%)	54 (78)
Prior CPI (%)	39 (57)
Prior anti-VEGF inhibitor (%)	21 (30)

Non-mesothelioma solid tumors included:

- Meningioma (9: 4 g*NF2*m, 4 s*NF2*m and 1 NF2m not detected);
- s*NF2*m Sarcoma (4);
- s*NF2*m Carcinoma of Unknown Primary; possibly mesothelioma of tunica vaginalis (1);
- s*NF2*m Serous Fallopian Tube Carcinoma (1);
- s*NF2*m Nasopharyngeal Cancer (1);
- s*NF2*m Papillary Renal Cell Cancer (1);
- s*NF2*m NSCLC; EHE (2);
- Biliary (1);
- Colon (1);
- g*NF2*m MPNST (1);
- g*NF2*m Schwannoma (1)

VT3989 tested at continuous and intermittent dosing schedules

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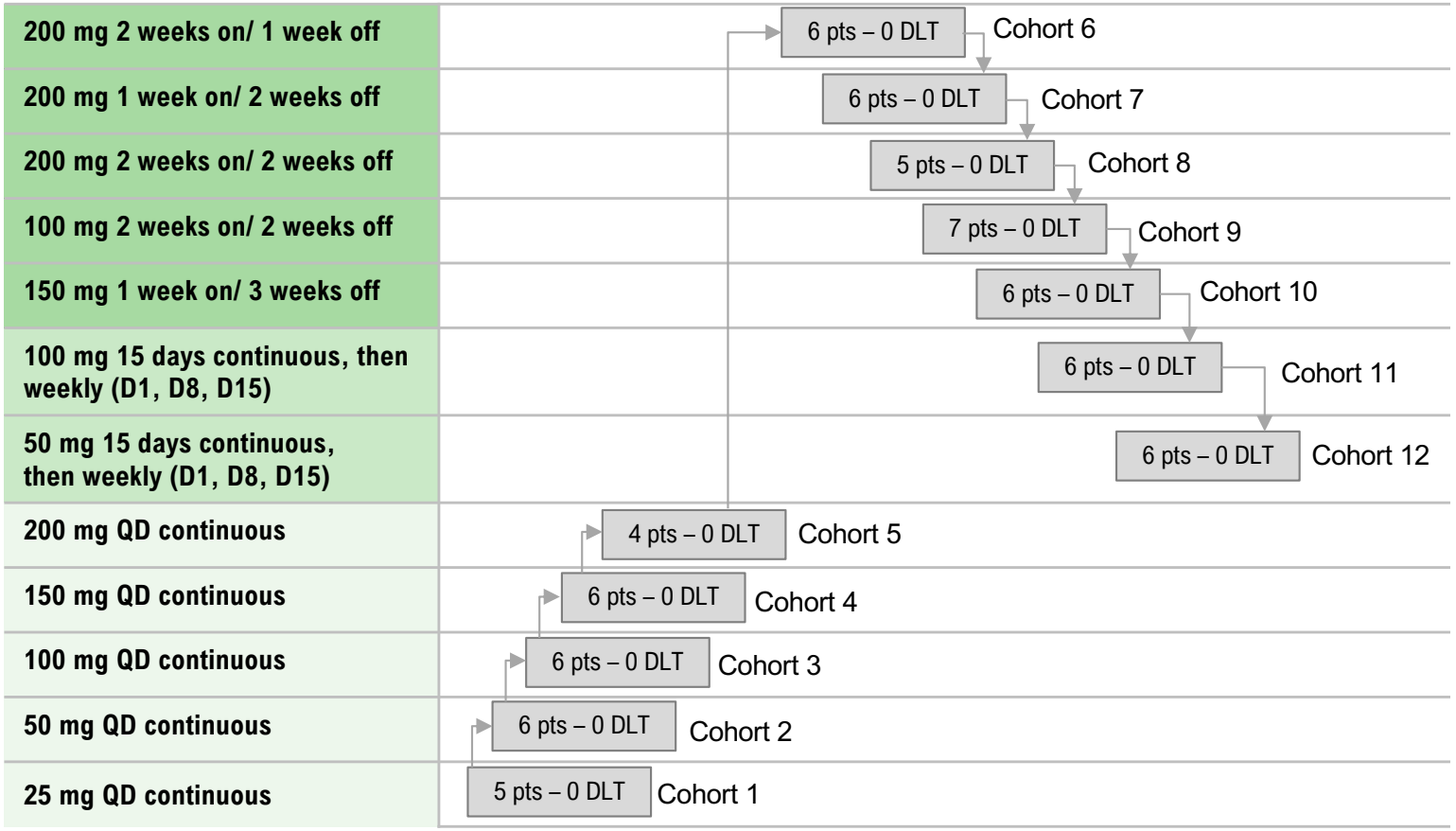

Dose escalation up to 200mg QD continuously.

Pre-clinical studies demonstrated comparable antitumor activity with continuous and intermittent dosing

Various intermittent dosing schedules were subsequently evaluated.

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VT3989 Safety Profile

Related Adverse Events ≥5 patients, worst grade by patient (N=69)

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Adverse Event	CTCAE Grade*				Total n (%)
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	
Albuminuria	11 (15.9)	23 (33.3)	3 (4.3)	0	37 (53.5)
Peripheral edema	20 (29)	4 (5.8)	1 (1.4)	0	25 (36.2)
Fatigue	9 (13)	7 (10.1)	1 (1.4)	0	17 (24.6)
Nausea	13 (18.8)	1 (1.4)	0	0	14 (20.3)
Increased ALT	6 (8.7)	1 (1.4)	1 (1.4)	0	8 (11.6)
Increased AST	5 (7.2)	2 (2.9)	1 (1.4)	0	8 (11.6)
Increased cholesterol	4 (5.8)	1 (1.4)	0	0	5 (7.2)
Anorexia	5 (7.2)	0	0	0	5 (7.2)
Hyperlipidemia	3 (4.3)	2 (2.9)	0	0	5 (7.2)
Periorbital edema	4 (5.8)	1 (1,4)	0	0	5 (7.2)

No dose-limiting toxicities observed

*No grade 5 AEs were observed

- Albuminuria is not graded by CTCAE; in this table, G1 albuminuria is defined as UACR >100-300, G2 >300-2200 and G3 >2200
- A possibly-related G4 event of cardiomyopathy was observed in a 82y male with advanced pleural mesothelioma and known coronary artery disease, hypertension, aortic regurgitation and mild renal dysfunction. Patient received150mg VT3989 QD for 7 months (11 cycles), when a symptom-driven cardiac evaluation led to a diagnosis of G4 dilated cardiomyopathy with no clear etiology

VT3989 Reversible albuminuria

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UACR mg/gm (n = 69)	Cohorts 1-8, 10 25-200 mg/day continuously or 150-200mg on 4 intermittent dosing schedules (n = 50)	Cohorts 9, 11, 12 50-100 mg on 2 intermittent dosing schedules (n = 19)
Median (min, max)	341.9 mg/gm (17, 2715.4)	60.4 mg/gm (7.55, 431.2)
Mean (SD)	649.9 mg/gm (744.9)	89.7 mg/gm (111.4)

- Preclinical toxicology in rats and monkeys demonstrated dose-related, reversible proteinuria. Electron microscopy showed effacement of podocytes, which is believed to be target-related.
- Albuminuria and proteinuria have not been associated with significant clinical symptoms or changes in serum creatinine, creatinine clearance, or serum albumin.
- VT3989 given at doses ≤100 mg on intermittent schedules results in less frequent and less severe albuminuria, which is reversible with dose reduction or interruption.
- **Albuminuria and proteinuria have been reversible in patients treated at all doses and schedules.**

UACR: Urine albumin-creatinine ratio

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VT3989 Pharmacokinetics

Continuous Daily Dosing

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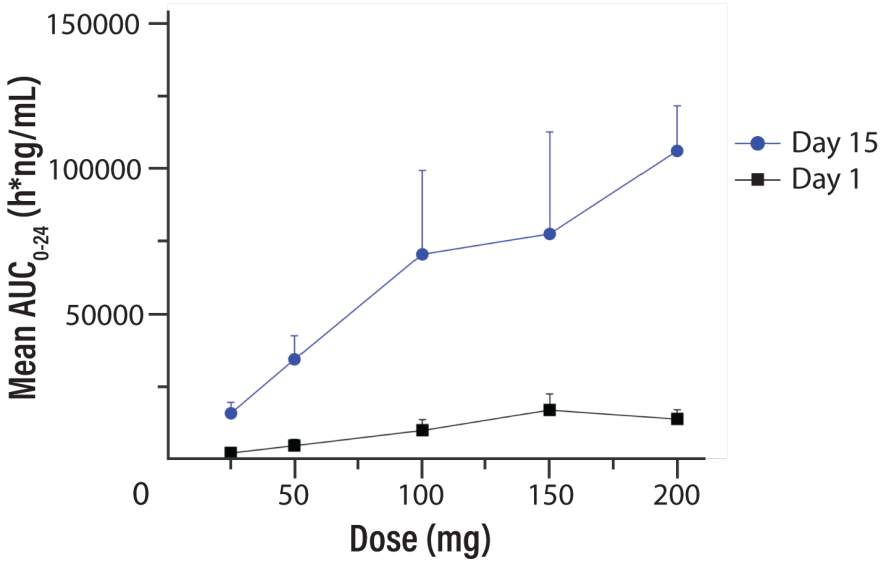
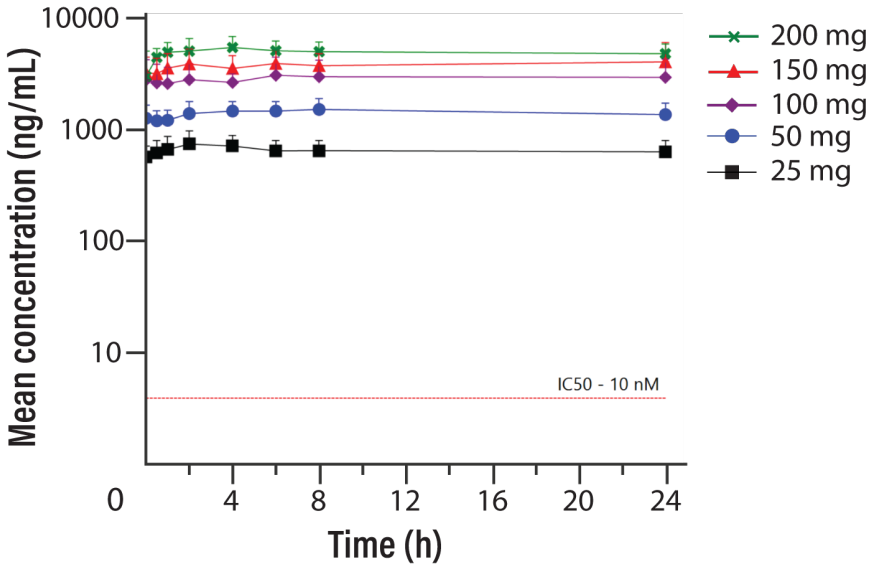
- VT3989 gives dose proportional exposure following oral administration
- VT3989 half-life is long, ~12-15 days
- PK exposure on day 15 is ~7x that on day 1

Mean VT3989 Plasma AUC_{last} vs. Dose



C1D15 Plasma Concentrations



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RECIST v1.1 Anti-Tumor Activity

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Initial Dose (mg/day) & Schedule	Tumor Type	*NF2* Mutation	RECIST v1.1 Response	% Change in Target Lesions	Treatment Duration (months)
200mg 2 weeks on, 2 weeks off	Dual Pleural/ Peritoneal Meso	No mutation	cPR	-81%	12+
50mg x 15 days, then once weekly	Peritoneal Meso	Unknown	cPR	-55%	6.5+
50mg continuously	Pericardial Meso	s*NF2*m	cPR	-47%	7.4
50mg continuously	Peritoneal Meso	No Mutation	cPR	-39%	7.6
100mg continuously	Peritoneal Meso	No Mutation	cPR	-39%	21+
200mg continuously	Sarcoma	sNF2m	cPR	-35%	8
150mg continuously	Peritoneal Meso	sNF2m	uPR	-30%	6.1
100mg continuously	Nasopharyngeal	sNF2m	SD	-24%	7.4
150 for 1 week on, 3 weeks off	EHE	Unknown	SD	-22%	9.5+

s*NF2*m: Somatic *NF2* mutation; cPR: confirmed partial response; uPR: unconfirmed PR; SD: stable disease

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Duration of treatment

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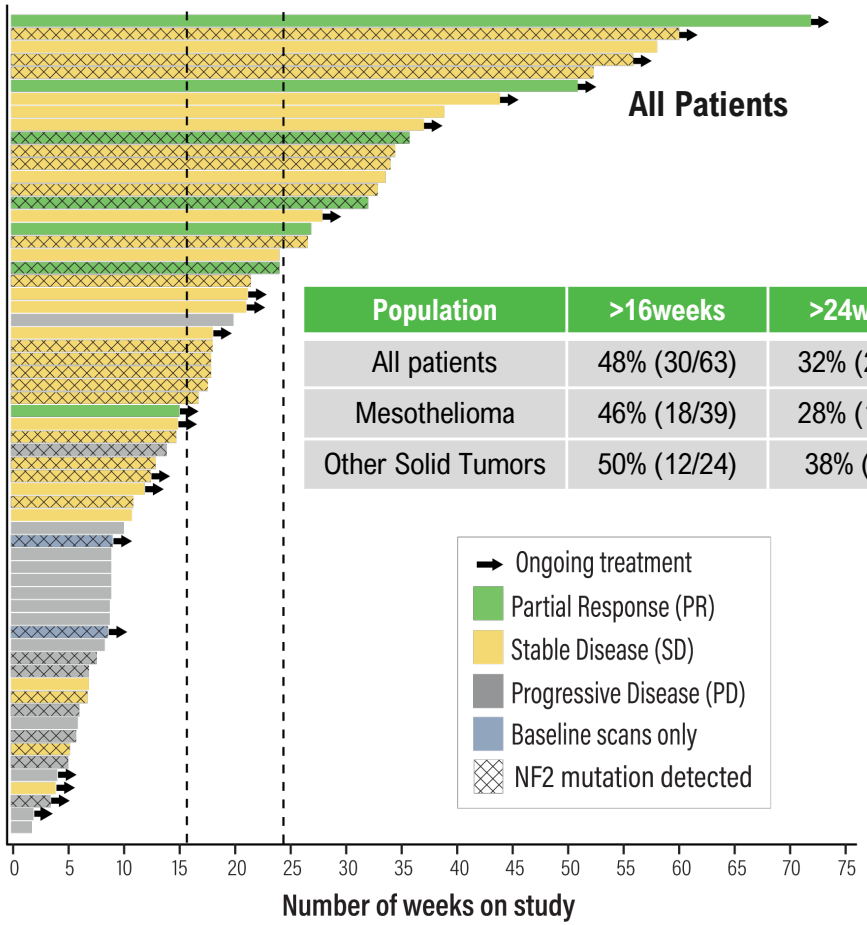
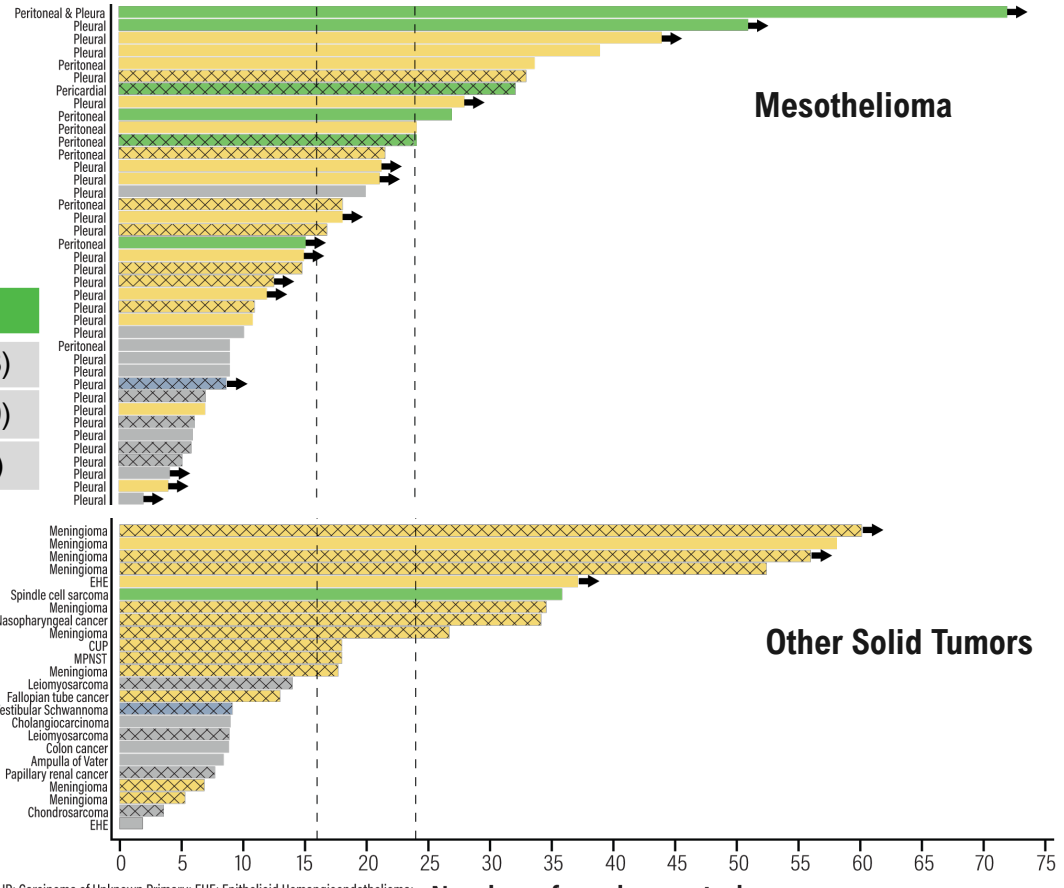


Population	>16weeks	>24weeks
All patients	48% (30/63)	32% (20/63)
Mesothelioma	46% (18/39)	28% (11/39)
Other Solid Tumors	50% (12/24)	38% (9/24)



CUP: Carcinoma of Unknown Primary; EHE: Epithelioid Hemangioendothelioma; MPNST: Malignant Peripheral Nerve Sheath Tumors of the Spine

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Antitumor activity by tumor type

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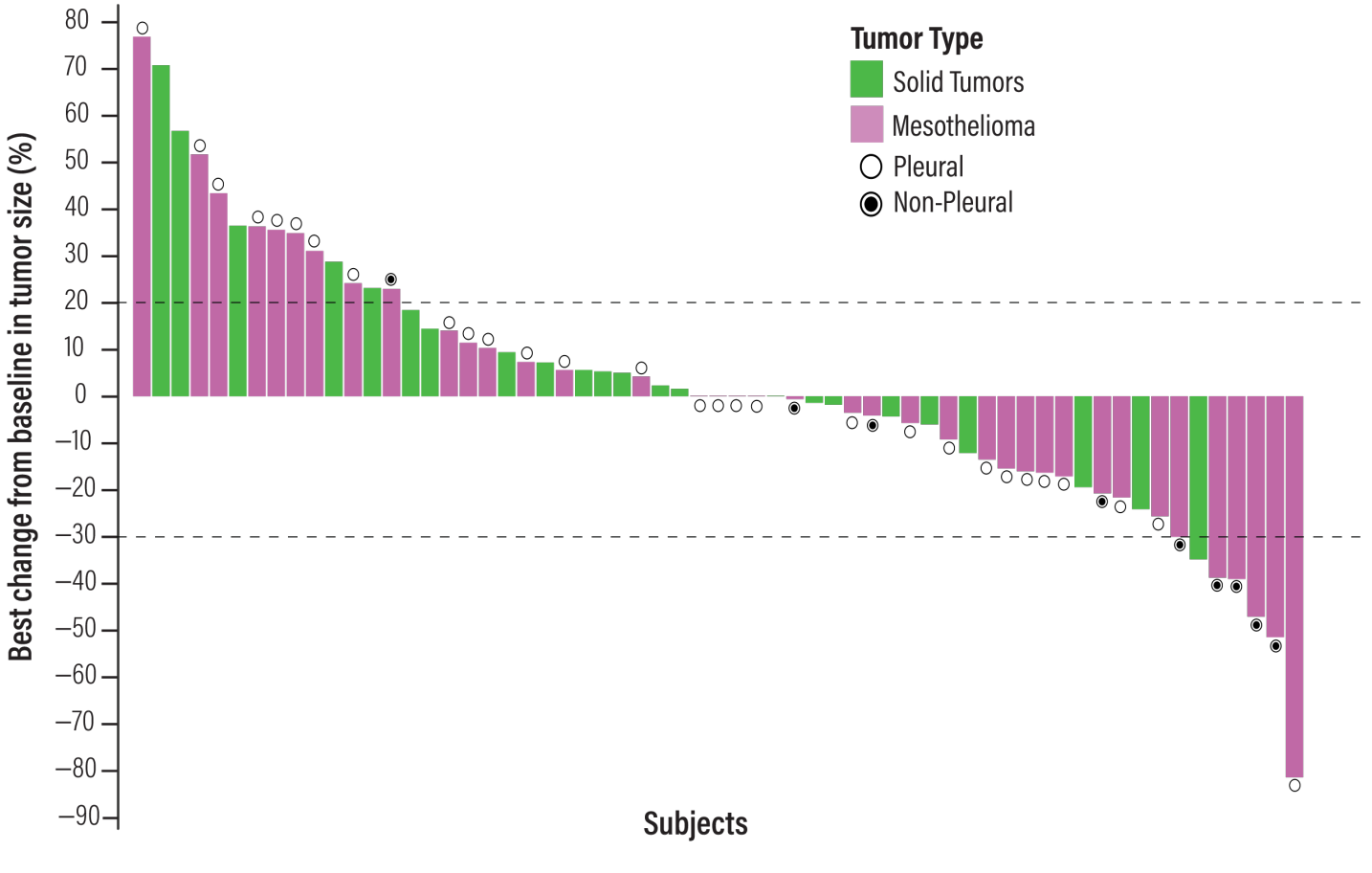
- **Responses seen across:**
  - **Tumor types**
  - *NF2* mutation

- 7 patients with measurable disease had RECISTv1.1 response
  - cPR (n=6)
  - uPR (n=1)

- 34 patients with measurable disease had SD as best response



Antitumor activity by NF2 mutation

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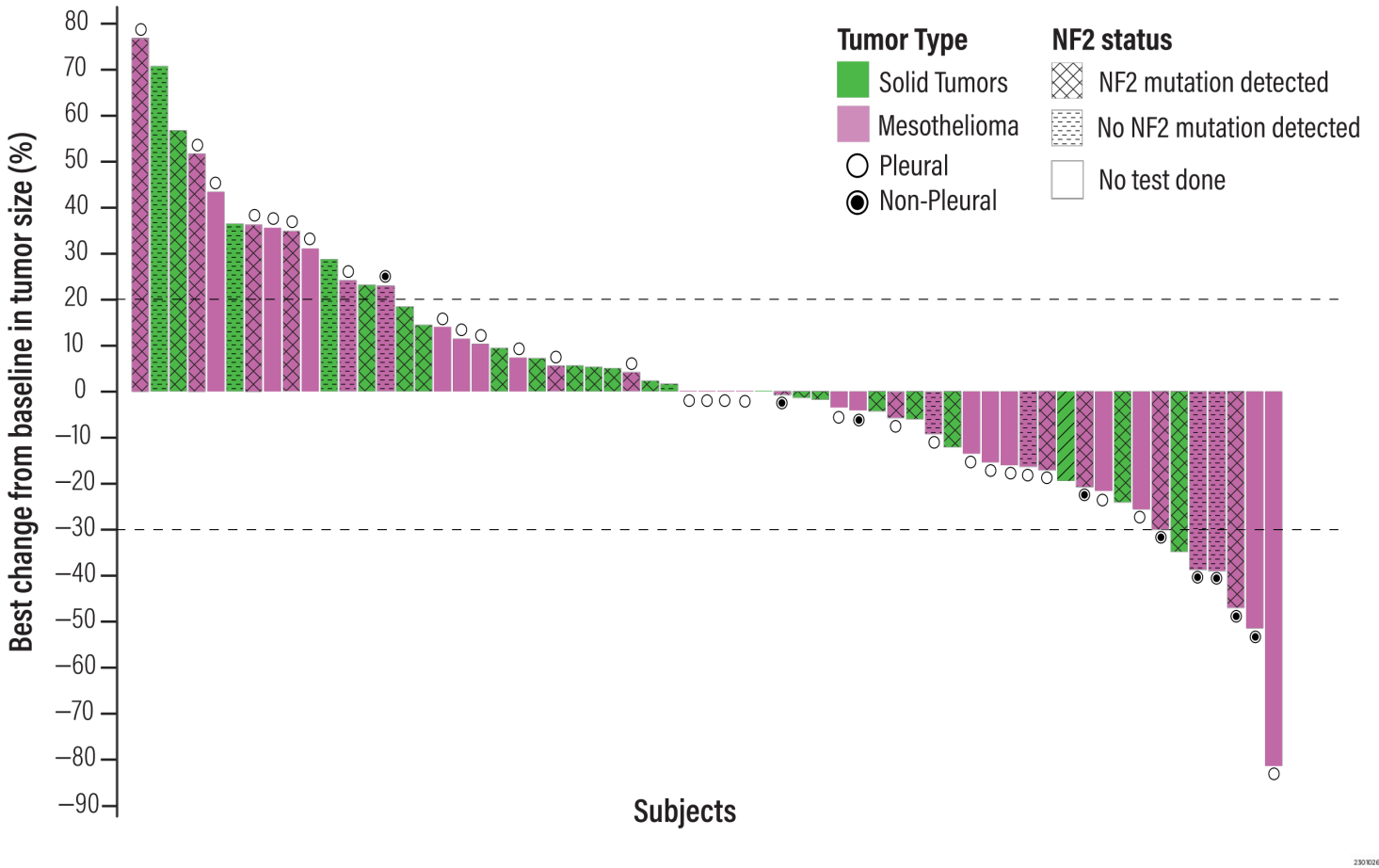
- **Responses seen across:**
  - Tumor types
  - ***NF2* mutation**

- 7 patients with measurable disease had RECISTv1.1 response
  - cPR (n=6)
  - uPR (n=1)

- 34 patients with measurable disease had SD as best response



Preliminary antitumor activity case study 1
Subject 102-1022

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22 y/o female with advanced Dual Pleural/Peritoneal Mesothelioma Without *NF2* mutation

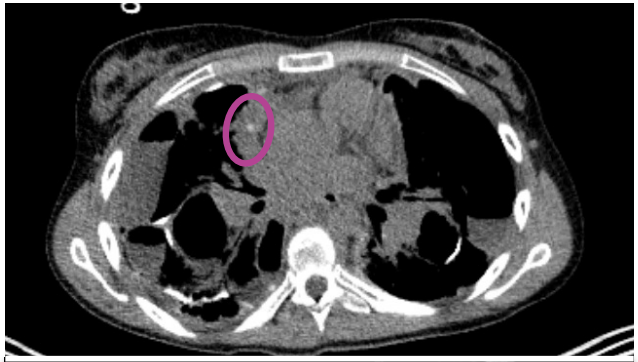
VT3989 25 mg PO QD, 2 weeks on/2 weeks off; 28-day cycle

Prior therapies

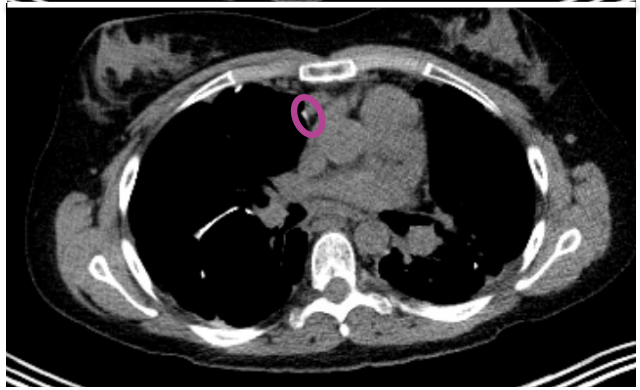
- Cisplatin + Pemetrexed + Bevacizumab
- Pemetrexed + Bevacizumab maintenance
- Ipilimumab + Nivolumab
- PIM kinase inhibitor TP-3654

RECIST sustained PR (–81.3%)
On treatment for 12+ months

Baseline
16 mm



C14D1
3 mm



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Preliminary antitumor activity case study 2
Subject 102-1007

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51 y/o male with advanced mesothelioma of peritoneum
Without *NF2* mutation

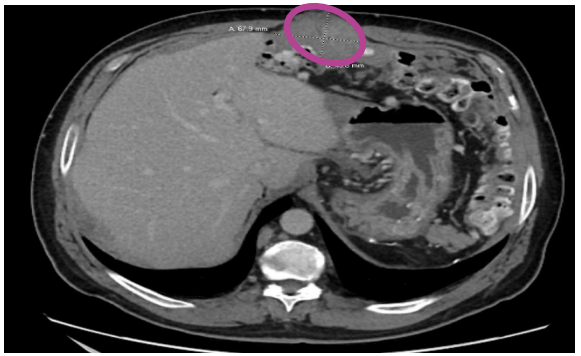
VT3989 50 mg PO QD; 21-day cycle

Prior therapies

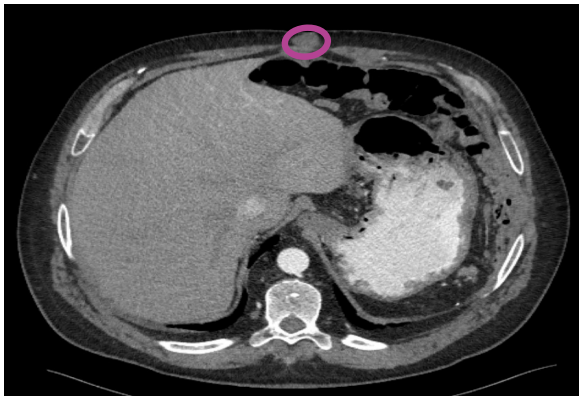
- Cisplatin + Pemetrexed
- Pembrolizumab
- Carboplatin + Pemetrexed
- Pemetrexed maintenance
- Ipilimumab + Nivolumab

RECIST sustained PR (–38.7%)
On treatment for 21+ months

Baseline
163 mm



C22D1
100 mm



Preliminary antitumor activity case study 3
Subject 102-1012

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55 y/o female with advanced high grade spindle cell sarcoma with somatic *NF2* mutation

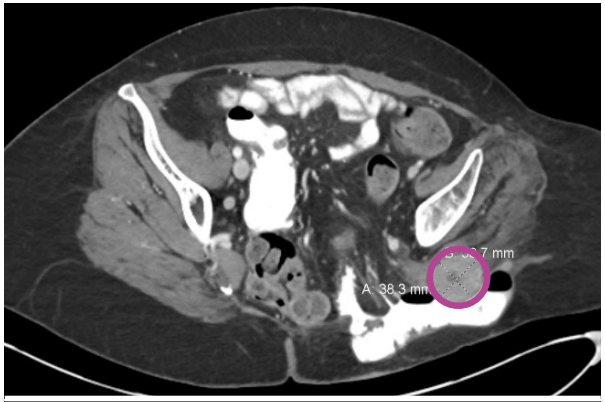
VT3989 150 mg PO QD, 2 weeks on/1 week off; 21-day cycle

Prior therapies

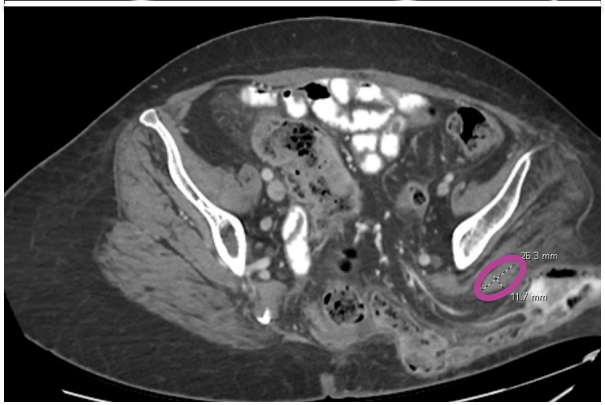
- Mesna + Adriamycin + Ifosfamide + Dacarbazine
- Mesna + Cytoxan + Vincristine + Actinomycin
- Ifosfamide
- Pazopanib
- Tazemetostat

RECIST confirmed PR (–34.8%)
On treatment for 8 months

Baseline
69 mm



C10D1
45 mm



Conclusions
Part 1 of the VT3989 FIH Phase I

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- VT3989 is safe and well tolerated.
- Durable anti-tumor activity observed in patients with advanced mesothelioma with or without *NF2* mutations and in other solid tumors with *NF2* mutations.
- Albuminuria is reversible with dose interruption/reduction and avoidable with doses 50-100 mg on intermittent schedules while maintaining anti-tumor activity.
- VT3989 demonstrated dose proportional PK exposures and a long half-life
- These data provide the first early clinical proof-of-concept for effectively drugging the Hippo-YAP-TEAD pathway.
- Dose optimization expansion cohorts are currently evaluating different doses/schedules in 2-stage designs

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