First-in-human phase 1 trial of VT3989, a first-in-class YAP/TEAD inhibitor in patients with advanced mesothelioma

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Background

VT3989 and the Hippo-Yap/TAZ-TEAD signaling pathway

Hippo signaling regulates transcription factors YAP and TAZ in response to diverse upstream signals

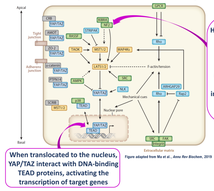


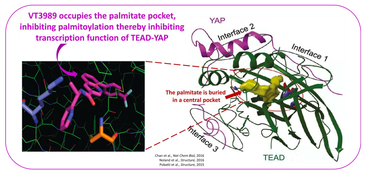
Figure adapted from Wu et al., Annu Rev Biochem, 2019

Hippo pathway dysfunction promotes activation of YAP/TAZ, resulting in uncontrolled proliferation and impaired differentiation

NF2 mutations, one mechanism by which Hippo control of YAP/TAZ is inactivated in tumors, are common in mesothelioma[1]

1. Creamey et al., Genome Med, 2022

Palmitoylation of a conserved cysteine is required for TEAD interaction with YAP



Chan et al., Nat Chem Biol, 2016
Noland et al., Structure, 2016
Pobbati et al., Structure, 2015

First-in class, first-in human Phase 1 Study of VT3989

Study Design

- Advanced refractory solid tumors, enriched for malignant pleural mesothelioma and other tumors with *NF2* mutations
- 3+3 dose escalation with dose expansion
- 3 or 4-week treatment cycles
- Response assessment every 8 to 9 weeks
- Key inclusion criteria:
  - ECOG PS 0-2
  - hemoglobin ≥ 8 g/dL, ANC ≥ 1.5 K/uL, platelets ≥ 100 K/uL, ALT/AST ≤ 2.5 x ULN, bilirubin ≤ 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

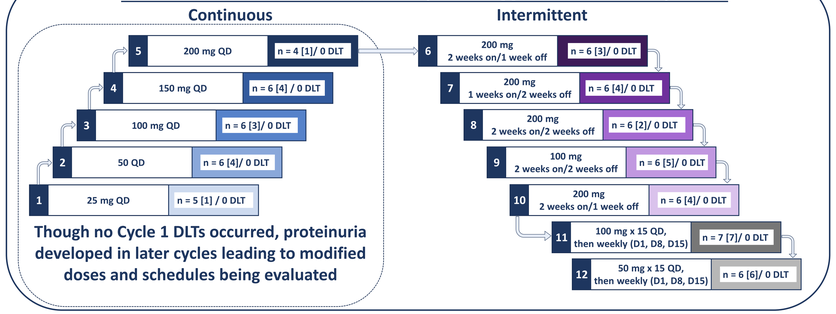
Study Endpoints

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

Secondary:
- Preliminary antitumor activity in *NF2* mutation tumors
- Pharmacokinetics
- Time to response and duration of response

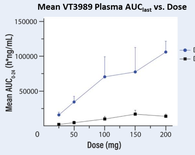
Exploratory:
- Hippo-Yap signaling in sequential tumor biopsies
- ctDNA changes

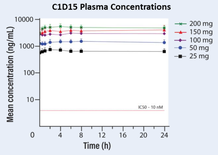
Dose cohorts and escalation schema, n = all patients [ ] = mesothelioma patients



Though no Cycle 1 DLTs occurred, proteinuria developed in later cycles leading to modified doses and schedules being evaluated

VT3989 Pharmacokinetics





- Dose-proportional exposure following oral administration
- Long half-life (approximately 12-15 days)
- Exposure on Day 15 is approximately 7x that of Day 1

First early clinical proof-of-concept that VT3989 inhibition of the Hippo-YAP-TEAD signaling pathway has antitumor efficacy

Durable activity seen in patients with advanced mesothelioma +/- *NF2* mutations

- Intermittent dosing of VT3989 at ≤100 mg results in less frequent/severe albuminuria which is reversible with dose reduction or interruption
- Dose-optimization expansion cohorts currently evaluating different doses/schedules in 2-stage designs
- Multivariate analyses underway to explore potential predictors of nephropathy

Baseline demographics and characteristics – mesothelioma patients

Baseline Demographics	N = 44 (%)
Median Age (range)	63.3 (21 - 83)
Gender	
Female (%)	19 (43)
Male (%)	25 (57)
Race	
White (%)	38 (86.4)
Black (%)	2 (4.5)
Other (%)	4 (9.1)
Ethnicity	
Hispanic (%)	4 (9.1)
ECOG Performance Status	
0 (%)	6 (13.6)
1 (%)	38 (86.4)

Baseline Characteristic	N = 44 (%)
Tumor Type	
Pleural	32 (72.7)
Peritoneal	10 (22.7)
Pericardial	1 (2.2)
Bicavitary	1 (2.2)
Molecular Profile	
NF2 Mutation	19 (43.2)
NF2 Wildtype	9 (20.5)
Unknown	16 (36.4)
Histology	
Epithelioid	35 (79.5)
Sarcomatoid	2 (4.5)
Biphasic/mixed	7 (15.9)
Prior Therapy (> 10 Patients)	
Median (Range)	3 (1 - 8)
Platinum-pemetrexed (%)	43 (98)
Immune checkpoint inhibitor (%)	39 (89)
Anti-VEGF antibody (%)	21 (48)
Gemcitabine (%)	11 (25)
Vinorelbine (%)	11 (25)

Results

Safety

Treatment-related adverse events in ≥ 5 patients (n = 44)*

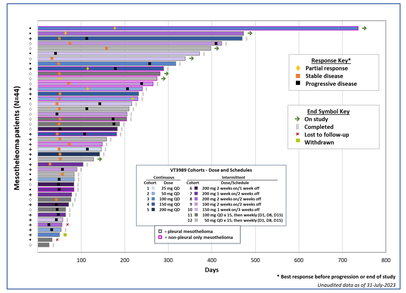
Adverse Event	CTCAE Grade 1 n	2 n	3 n	4 n	Total n (%)
Albuminuria	11	14	2	0	27 (61.6)
Proteinuria	14	12	0	0	26 (59.1)
Fatigue	9	4	1	0	14 (31.8)
Peripheral edema	10	3	0	0	13 (29.5)
Nausea	8	1	0	0	9 (20.5)
Increased ALT	4	1	1	0	6 (13.6)
Increased AST	4	1	1	0	6 (13.6)
Anemia	2	3	0	0	5 (11.4)
Decreased appetite	5	0	0	0	5 (11.4)

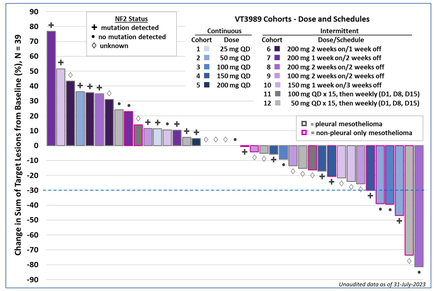
Albuminuria

	UACR (mg/gm) Cohorts 1-8, 10 (n = 26)	Cohorts 9, 11, 12 (n = 18)
Median (min, max)	255.7 (17.0, 2715.4)	86.4 (2.94, 2000.0)
Mean (SD)	654.3 (758.3)	297.8 (517.6)

- Albuminuria/proteinuria have not been associated with significant clinical symptoms or changes in serum creatinine, creatinine clearance, or serum albumin

Time on study and antitumor activity



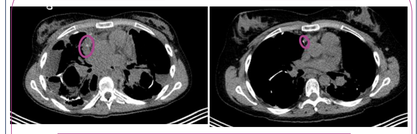


Preliminary antitumor activity

Case Study 1

- 22 year-old female with advanced dual pleural/peritoneal mesothelioma; no *NF2* mutation
- Prior therapies:
  - cisplatin + pemetrexed + bevacizumab
  - pemetrexed + bevacizumab maintenance
  - ipilimumab + nivolumab
  - PIM kinase inhibitor TP-3654
- Received VT3989 25 mg PO QD, 2 weeks on/2 weeks off; 28-day cycle

Baseline = 16 mm | C14 D1 = 3 mm

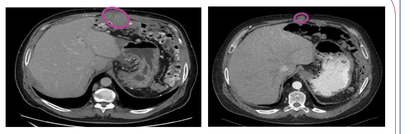


RECIST 1.1 sustained PR (-81.3%)
On study for 17+ months

Case Study 2

- 51 year old male with advanced peritoneal mesothelioma; no *NF2* mutation
- Prior therapies:
  - cisplatin + pemetrexed
  - pembrolizumab
  - carboplatin + pemetrexed
  - pemetrexed maintenance
  - Ipilimumab + Nivolumab
- Received VT3989 50 mg PO QD; 21-day cycle

Baseline = 163 mm | C22 D1 = 100 mm



RECIST 1.1 sustained PR (-38.7%)
On study for 25+ months

ClinicalTrials.gov NCT04665206

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