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

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 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.

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1. Creaney et al., Genome Med, 2022

Figure adapted from Ma et al., Annu Rev Biochem, 2019
VT3989 inhibits TEAD-YAP

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.

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

- 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. Tang et al., *Mol Cancer Ther*, 2021
4. Pobatti et al., *Structure*, 2015
First-in-class First-in-human Phase 1 study of VT3989 in patients with advanced solid tumors

Dose escalation, 3+3 dose escalation with “back fill” slots

- VT3989 DL1
- VT3989 DL2
- VT3989 DL3
- VT3989 DL4
- VT3989 DL5

Dose expansion, 2-stage design

- MTD RP2D

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/dL

*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

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

VT3989

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
Baseline Patient Characteristics
Part 1, Cohorts 1-12

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n=69)</th>
<th>Characteristic</th>
<th>(n=69)</th>
<th>Tumor Types</th>
<th>33 (48)</th>
<th>8 (12)</th>
<th>11 (16)</th>
<th>58 (84)</th>
<th>11 (16)</th>
<th>54 (78)</th>
<th>39 (57)</th>
<th>21 (30)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.5 (21-83)</td>
<td>Tumor Types</td>
<td>Peritoneal Mesothelioma</td>
<td>33 (48)</td>
<td>8 (12)</td>
<td>11 (16)</td>
<td>58 (84)</td>
<td>11 (16)</td>
<td>54 (78)</td>
<td>39 (57)</td>
<td>21 (30)</td>
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<tr>
<td>Gender</td>
<td>Female (49)</td>
<td>Peritoneal &amp; Peritoneal Mesothelioma</td>
<td>1 (1)</td>
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<td>Male (51)</td>
<td>Pericardial Mesothelioma</td>
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<td>Race</td>
<td>White (87)</td>
<td>Meningioma</td>
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<td>31 (46)</td>
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<td>Other Solid Tumor</td>
<td>13 (19)</td>
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<td>Ethnicity</td>
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<td>ECOG Performance Status</td>
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<td>Molecular Profile</td>
<td>NF2 Mutations</td>
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<td>Somatic</td>
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<td>Prior Therapy</td>
<td>Median (Range)</td>
<td>3 (0-8)</td>
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<td>Prior chemotherapy (%)</td>
<td>54 (78)</td>
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<td>Prior CPI (%)</td>
<td>39 (57)</td>
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<td></td>
<td>Prior anti-VEGF inhibitor (%)</td>
<td>21 (30)</td>
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</tbody>
</table>

Non-mesothelioma solid tumors included:
- Meningioma (9: 4 gNF2m, 4 sNF2m and 1 NF2m not detected);
- sNF2m Sarcoma (4);
- sNF2m Carcinoma of Unknown Primary; possibly mesothelioma of tunica vaginalis (1);
- sNF2m Serous Fallopian Tube Carcinoma (1);
- sNF2m Nasopharyngeal Cancer (1);
- sNF2m Papillary Renal Cell Carcinoma (1);
- sNF2m NSCLC; EHE (2);
- Biliary (1);
- Colon (1);
- gNF2m MPNST (1);
- gNF2m Schwannoma (1)

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
VT3989 tested at continuous and intermittent dosing schedules

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.
**VT3989 Safety Profile**

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

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

*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 received 150mg 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

- 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 \( \leq 100 \text{ mg} \) 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.

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

UACR: Urine albumin-creatinine ratio
VT3989 Pharmacokinetics
Continuous Daily Dosing

- 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**

- IC$_{50}$ ~ 10 nM
## RECIST v1.1 Anti-Tumor Activity

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

sNF2m: Somatic NF2 mutation; cPR: confirmed partial response; uPR: unconfirmed PR; SD: stable disease
### Duration of treatment

**All Patients**

<table>
<thead>
<tr>
<th>Population</th>
<th>&gt;16 weeks</th>
<th>&gt;24 weeks</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
<td>48% (30/63)</td>
<td>32% (20/63)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>46% (18/39)</td>
<td>28% (11/39)</td>
</tr>
<tr>
<td>Other Solid Tumors</td>
<td>50% (12/24)</td>
<td>38% (9/24)</td>
</tr>
</tbody>
</table>

**Mesothelioma**

- Ongoing treatment
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Baseline scans only
- NF2 mutation detected

**Other Solid Tumors**
Antitumor activity by tumor type

- 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

- 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

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
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
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
Conclusions
Part 1 of the VT3989 FIH Phase I

- 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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ALL PATIENTS AND THEIR CAREGIVERS

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MGH: Susan Symes
U Chicago: Andrew McGettigan, Gairta Porroga, RN
Monash Medical Centre: Amy Louise Body BMedSc, MBBS, Penny Macguire
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