VV1 oncolytic virus + cemiplimab + ipilimumab in patients with melanoma or NSCLC

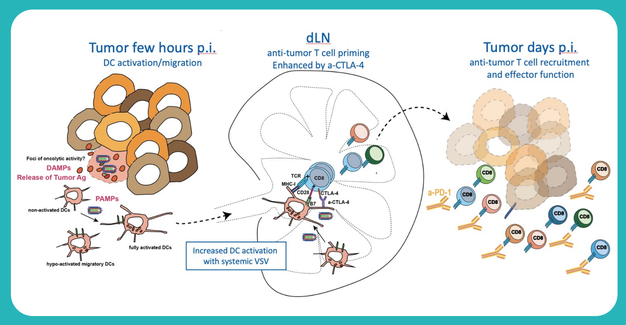
Abstract: TPS9595

ASCO 2022

Background and rationale

- Oncolytic VV1 is derived from VSV, a low seroprevalence RNA virus
- Engineered to express human IFNβ to enhance cellular anti-tumor immune responses and tumor selectivity
  - VV1 replicates selectively in (and kills) human cancer cells
- Clinical anti-tumor activity with/without a CPI in several malignancies
- Non-clinical data show putative synergistic mechanism (Fig. 1):
  - Synergy in MC38, B16F10 melanoma and CMT64 lung adenocarcinoma between VV1 and an anti-CTLA4 antibody, in addition to anti-PD-1 (Fig. 2, 3 & 5)
  - Triple combo boosts T cell priming against the B16F10 and CMT64 neo-antigen peptides in TILs and tumor-draining LNs (Fig. 4 & 6)
  - Triple combination significantly boosts CD8 infiltration in CMT64 lung cancer model (Fig. 6)

Fig 1. Triple combination hypothetical mechanism of action



VSV induces release of tumor-antigens and has strong adjuvant properties activating DCs. Anti-CTLA-4 increases T cell priming in the tumor-draining LN. Anti-PD-1 increases T cell function in the TME.

Fig 2. Triple combination Inhibits MC38 tumor growth and increases survival

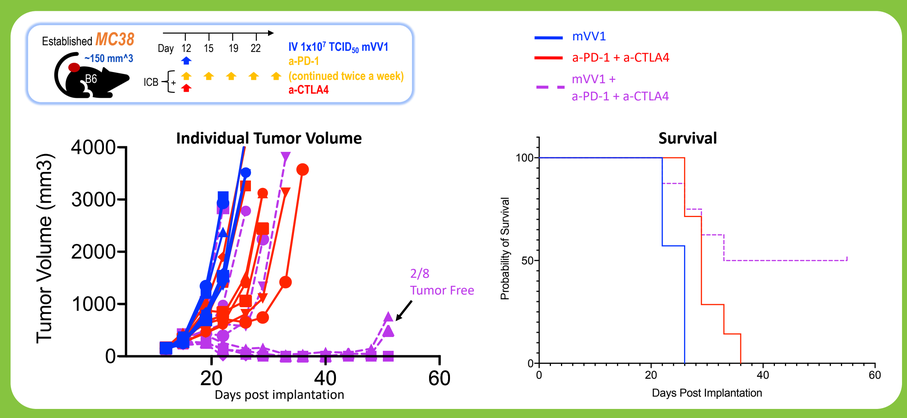


Fig 3. Triple combination inhibits B16F10 melanoma tumor growth and increases survival

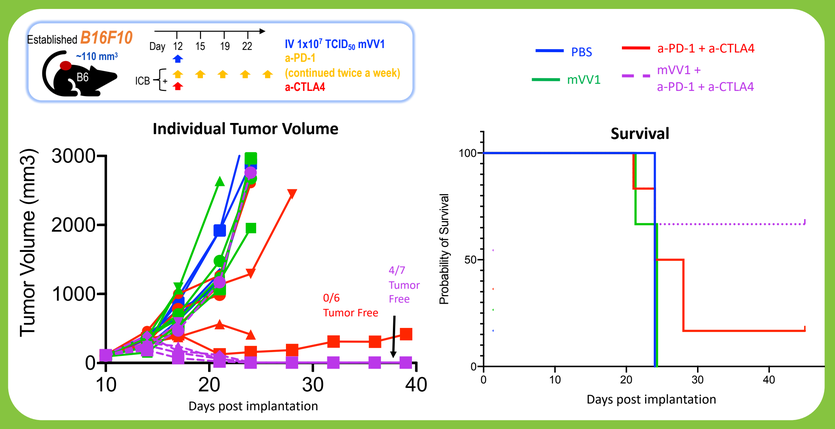


Fig 4. Antigen-specific response in tumor-draining lymph nodes of B16F10 melanoma model

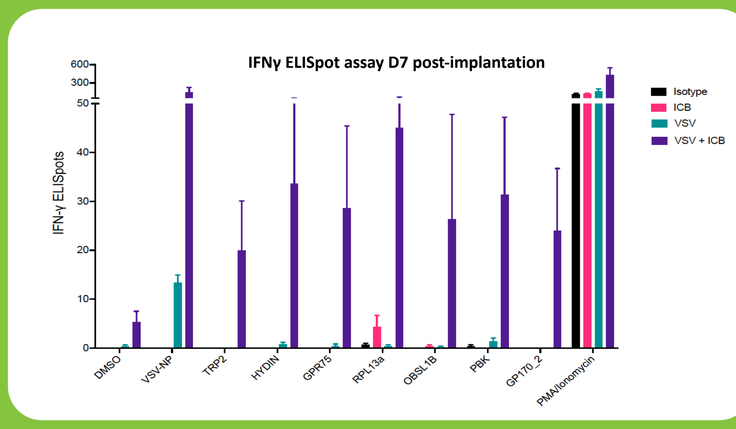


Fig 5. Triple combination inhibits CMT64 lung adenocarcinoma tumor growth

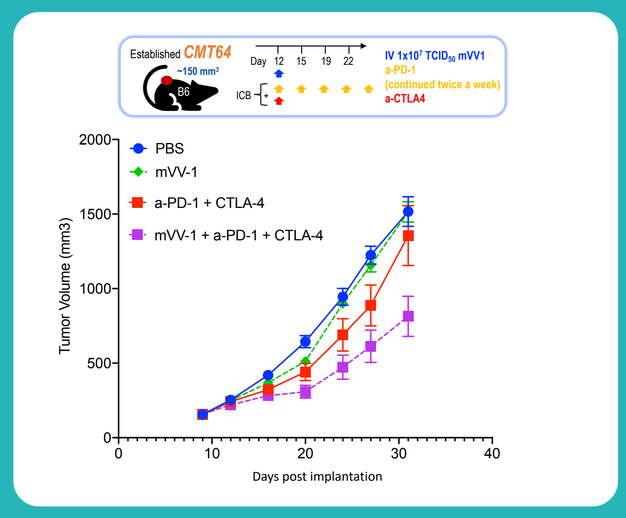
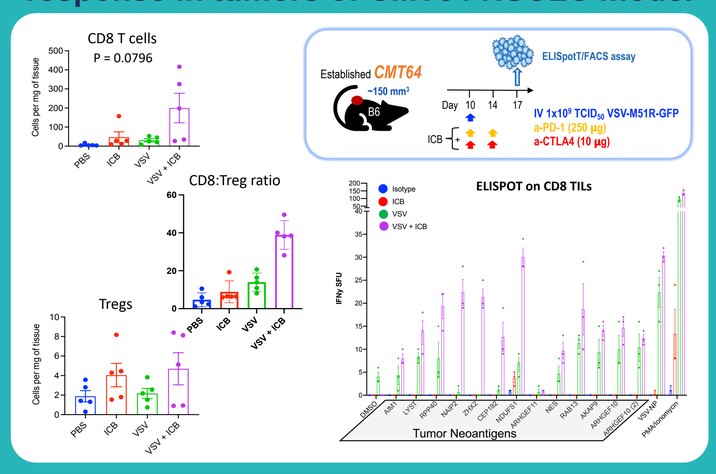


Fig 6. Increase of antigen-specific CD8 T cell response in tumors of CMT64 NSCLC model



Methods

- Open label, Simon 2-stage study, enrolling melanoma and NSCLC patients (Fig. 7)
- Doublet melanoma cohorts with serial biopsies:
  - one dose of IV VV1 + IV cemiplimab
  - one dose of IV VV1 + IT VV1 + IV cemiplimab
- Triplet cohorts:
  - Following ≥6 melanoma patients treated safely across the doublet cohorts – 2nd line one dose of IV VV1 + one dose IV ipilimumab + IV cemiplimab (with serial biopsies)
  - Following ≥6 melanoma patients treated safely in triplet cohort - 1st line NSCLC patients one dose of IV VV1 + one dose IV ipilimumab + IV cemiplimab
- All cohort decisions are guided by a DRC
- IV cemiplimab Q3W until confirmed PD or intolerable toxicity
- Response assessed W7 then Q9W per RECIST v1.1

Study objectives

PRIMARY

- Preliminary anti-tumor activity in each study cohort as measured by ORR

SECONDARY

- Safety and tolerability of VV1 + cemiplimab
- Systemic PK of VV1 + cemiplimab
- Pharmacodynamics of VV1 measured by serum IFNβ expression
- Preliminary clinical activity of each cohort [PFS, DoR, DCR and OS]
- Safety and efficacy of administration of VV1, cemiplimab, and ipilimumab

EXPLORATORY

- Immunocyte infiltrate in select pre- and post-treatment tumor specimens
- Time course of viremia, viral shedding, and virus persistence
- Effect on host peripheral blood immunocyte expansion/suppression
- Immunogenicity measured by anti-drug antibodies to cemiplimab + VV1
- Ability of ruxolitinib to mitigate the risk of IFNβ toxicity

Fig 7. Proof-of-concept optimization of triple combination in clinical study design

Simon stage 1		Simon stage 2
2L Melanoma (after PD on prior CPI) IV VV1 1.0x10^{11} TCID$_{50}$ D1 + IV cemiplimab 350 mg D8 (n=10)	2/10 ORR	2L Melanoma (after PD on prior CPI) IV VV1 1.0x10^{11} TCID$_{50}$ D1 + IV cemiplimab 350 mg D8 (n=11, total 21)
2L Melanoma (after PD on prior CPI) IV VV1 1.0x10^{11} TCID$_{50}$ D1 + IT VV1 1.0x10^{9} TCID$_{50}$ D1 + IV cemiplimab 350 mg D8 (n=10)	2/10 ORR	2L Melanoma (after PD on prior CPI) IV VV1 1.0x10^{11} TCID$_{50}$ D1 + IT VV1 1.0x10^{9} TCID$_{50}$ D1 + IV cemiplimab 350 mg D8 (n=11, total 21)
DRC approval		
2L Melanoma (after PD on prior CPI) IV VV1 1.0x10^{11} TCID$_{50}$ D1 + IV ipilimumab* 50 mg D1 + IV cemiplimab 350 mg D8 (n=10)	2/10 ORR	2L Melanoma (after PD on prior CPI) IV VV1 1.0x10^{11} TCID$_{50}$ D1 + IV ipilimumab* 50 mg D1 + IV cemiplimab 350 mg IV D8 (n=11, total 21)
DRC approval		
1L NSCLC PD-L1 ≥50% IV VV1 1.0x10^{11} TCID$_{50}$ D1 + IV ipilimumab* 50 mg D1 + IV cemiplimab 350 mg D8 (n=9)	5/9 ORR	1L NSCLC PD-L1 ≥50% IV VV1 1.0x10^{11} TCID$_{50}$ D1 + IV ipilimumab* 50 mg D1 + IV cemiplimab 350 mg D8 (n=13, total 22)

* Flat dose of ipilimumab 50 mg is equivalent to 1 mg/kg Q6W

Key inclusion criteria

- Histologically confirmed diagnosis of:
  - Cutaneous melanoma
  - Non-small cell lung cancer
- Treated with prior anti-PD-(L)1 therapy
- ≥18 years, ECOG PS 0 or 1
- Measurable disease by RECIST v1.1
- Willingness to provide biological samples
- Absence of active CNS involvement
- Adequate organ function

Key exclusion criteria

- Availability of acceptable curative therapy
- Recent or ongoing serious infection
- Ocular, mucosal or acral melanoma
- Any concomitant serious health condition
- Prior therapy within stated timeframes:
  - Small molecules ≤2 weeks or 5 x $t_{1/2}$
  - Chemotherapy ≤3 weeks or 5 x $t_{1/2}$
  - Radioimmunoconjugates ≤6 wks or 5 x $t_{1/2}$
- Organ-threatening autoimmune disorders
- Immunodeficiency or immunosuppression
- History of Grade 3-4 irAE from prior CPIs
- Current or historic pneumonitis requiring steroids
- High-volume disease

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NCT04291105

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Abbreviations: 1L= first line; 2L-second line; CPI=checkpoint inhibitor; CTLA4=cytotoxic T-lymphocyte-associated protein 4; DC=dendritic cells; DCR=disease control rate; DoR=duration of response; DRC=data review committee; ECOG=Eastern Cooperative Oncology Group; ELISpot=enzyme-linked immune absorbent spot; FACS=fluorescent-activated cell sorting; ICB= immune checkpoint blockade; IFN=interferon; irAEs=infusion-related adverse events; IV=intravenous; LN=lymph node; NSCLC=non-small cell lung cancer; ORR=overall response rate; OS=overall survival; PBS=phosphate-buffered saline; PD-(L)1= programmed death-(ligand)1; PD=progressive disease; PFS=progression-free survival; PK=pharmacokinetics; QxW= every (x) weeks; RECIST=response evaluation criteria in solid tumors; RNA=ribonucleic acid; t1/2 =half-life; TCID50=median tissue culture infectious dose; TILs=tumor infiltrating lymphocytes; TME=tumor microenvironment; VSV=vesicular stomatitis virus; VV1=Voyager V1.

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