

HSV1716 (SEPREHVIR®)

NIH RAC

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**Wexner
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Current Primary Study Team

Virttu Biologics, Ltd (Glasgow, U.K.)

- Steven Powell (CEO)
- Robert Spavin (COO)
- Joe Conner (CSO)
- Sue Goldsborough (CMO)
- Kathleen Simpson (Product Manager)

Cincinnati Children's (Cincinnati, OH)

- Jim Geller, MD (site PI)
- Marianne Brunner (regulatory specialist)
- Beth Stockman (research nurse)
- Alexander Towbin (diagnostic radiologist)
- John Racadio (interventional radiologist)

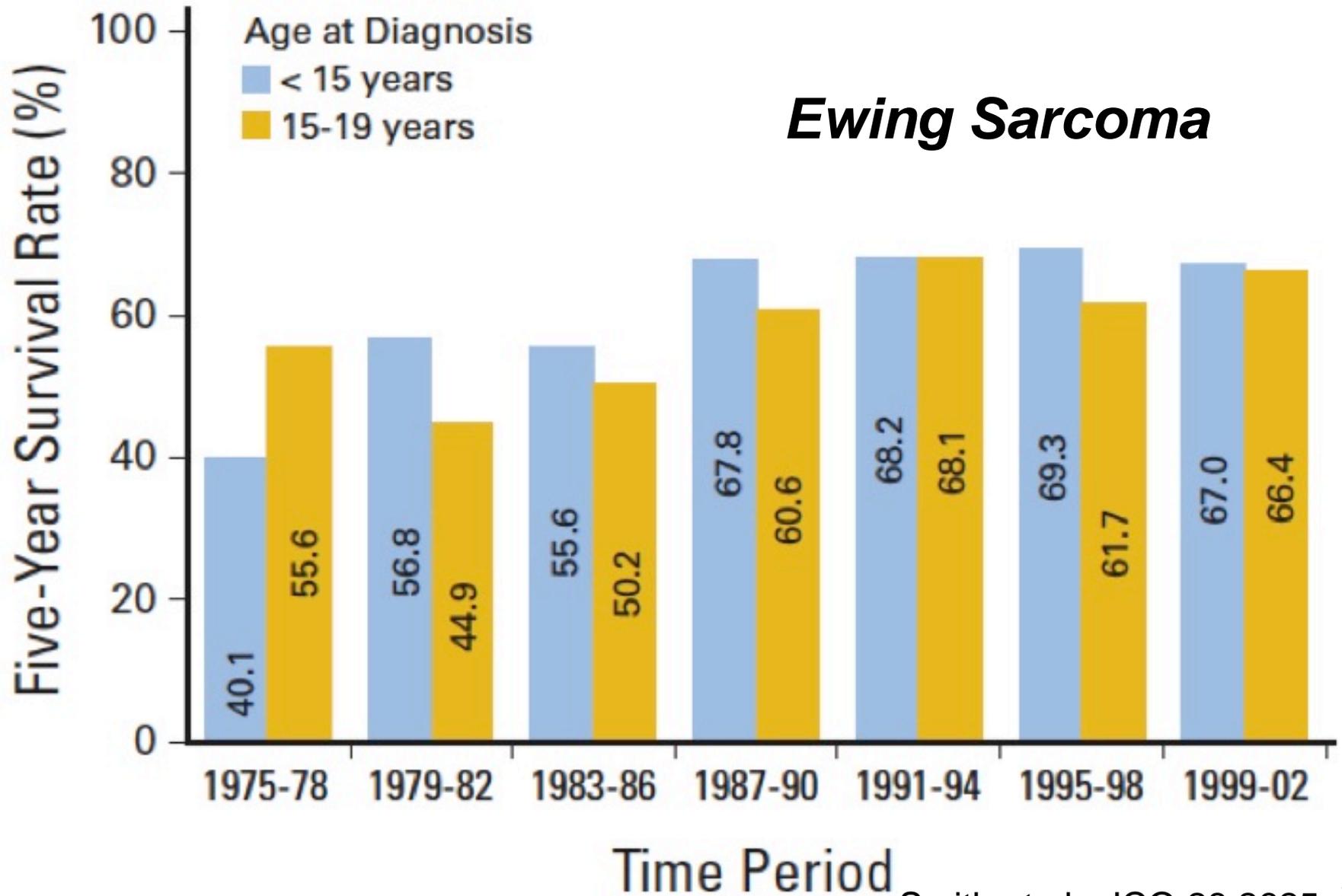
Nationwide Children's (Columbus, OH)

- Timothy Cripe, MD., PhD (Sponsor-investigator)
- Mark Currier (Biosafety officer, translational scientist)
- Michele Vaughan (CRO Director)
- Jenny Notestine (CRA)

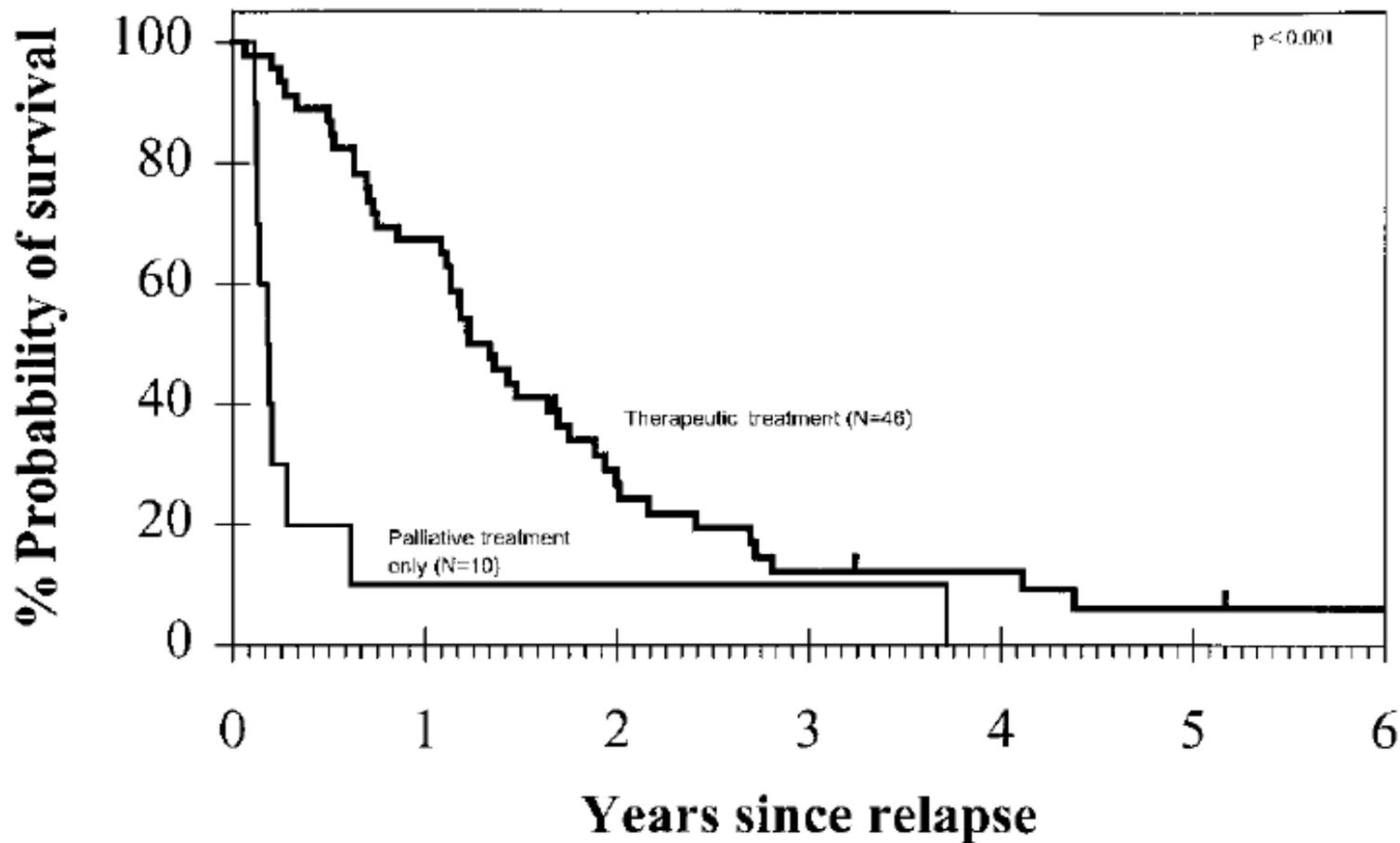
Outline

- Childhood/Adolescent/Young Adult sarcoma
 - Ewing sarcoma as an example
- Review of other relevant oncolytic virus studies
 - Pediatric
 - HSV
- HSV1716 Background
- Study Update
- Proposed major amendment

Stalled Progress in Childhood Cancer



Survival After Relapsed Ewing's Sarcoma



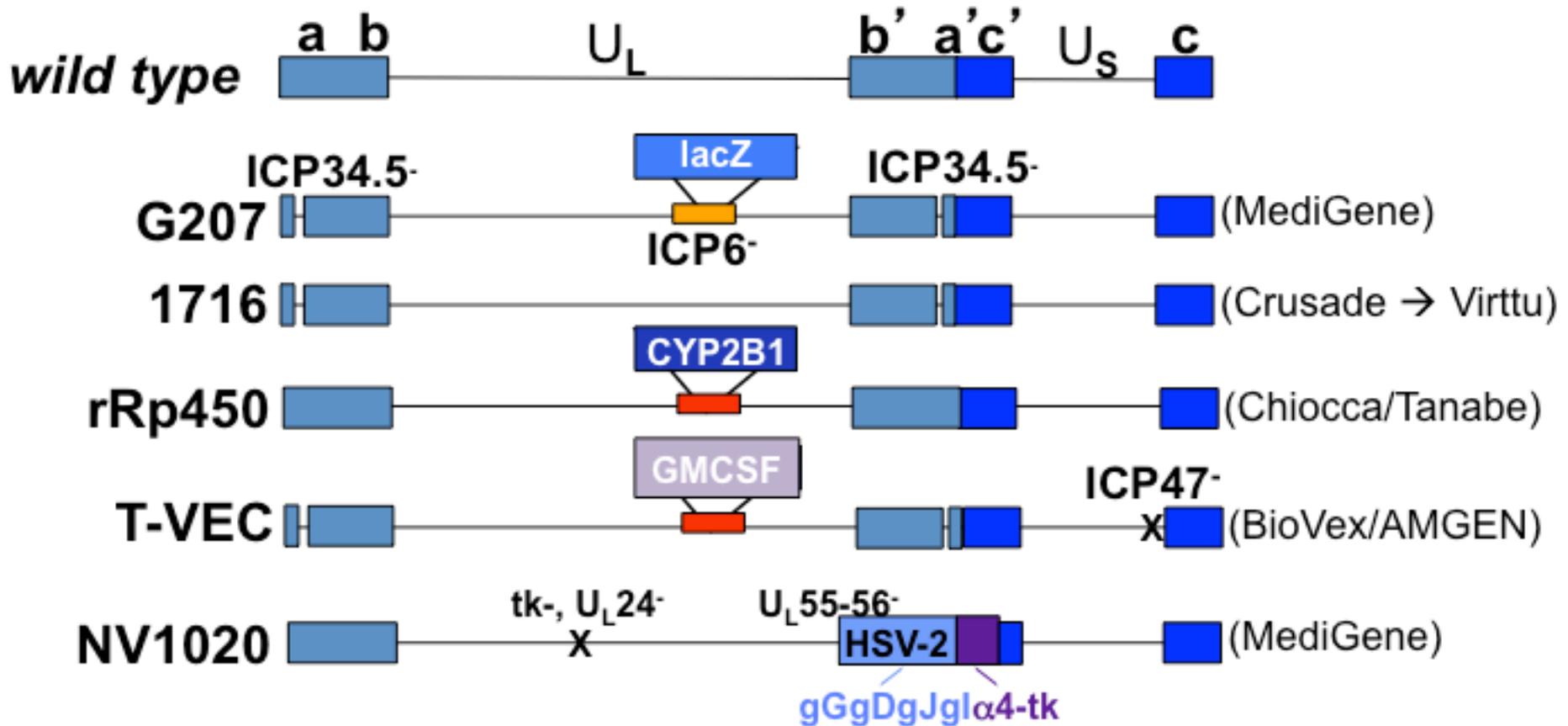
Shankar et al., Med Pediatr Oncol 40:141-147, 2003

Oncolytic Virotherapy

- The use of live viruses to:
 - Infect and kill (lyse) tumor cells
 - Induce an antitumor immune response
 - Express foreign transgenes
- HSV studies (clinicaltrials.gov, searched on May 23, 2013)
 - G207 (2 completed)
 - NV1020 (2 completed, intrahepatic artery)
 - rRp450 (1 recruiting, intrahepatic artery)
 - HF10 (1 recruiting, intratumoral)
 - T-VEC (5 studies, intratumoral)
 - HSV1716 (2 recruiting)
 - ❖ 6 completed in Europe, not on clinicaltrials.gov

OPEN PEDIATRIC CLINICAL TRIALS	SVV-001 /NTX-010 (ADVL0911) Neotropix/CTEP	Reolysin (ADVL1014) Oncolytics Biotech	HSV1716 Virttu Biologics	JX-594 Jennerex Biotherapeutics
Date opened for accrual	March, 2010	March, 2011	February, 2010	December, 2010
Locations	COG Phase I sites	COG Phase I sites plus selected others	Cincinnati Children's, Nationwide Children's (pending IRB)	Cincinnati Children's, Texas Children's
Age (yrs)	3-21	3-21	7-30	2-21
Tumor type	Neuroendocrine tumors	Non-CNS solid tumors	Non-CNS solid tumors	Non-CNS solid tumors
Route	Intravenous	Intravenous	Intratumoral, intravenous	Intratumoral
Minimal size of lesion	Measurable or evaluable	Measurable or evaluable	1.8 cm (each dimension) or 3 mL for intratumoral; larger for dose level 3; measurable for IV	1 cm
Dose levels	10 ⁹ vp/kg 10 ¹⁰ vp/kg 10 ¹¹ vp/kg ←	3 x 10 ⁸ TCID ₅₀ /kg 5 x 10 ⁸ TCID ₅₀ /kg ←	1 x 10 ⁵ i.u. 2 x 10 ⁶ i.u. (ITu, IV) ← 1 x 10 ⁷ i.u. (ITu, IV)	10 ⁶ pfu/kg 10 ⁷ pfu/kg 10 ⁸ pfu/kg ←
Number of Injections	A: Single 1-hour infusion B: Days 8 and 29	1-hour infusion daily for 5 days; repeat every 28 days x 12 courses	1 tumor site, up to 3 sites at highest dose; if response, repeat every 28 days x 3 (ITu only; IV pending review)	1-3 tumor sites; if response, repeat every 28 days x 3
Combination	Metronomic CPM + IV CPM in PART B	Metronomic CPM at higher dose ←	None	None
Contact restrictions	Until viral clearance; bleach toilet	3 weeks after each infusion	4 days	7 days
Hosp admission	1 day	Not required	Overnight after injection	Day before and after 7

Oncolytic HSV-1s in Clinical Trials



(Deletion of internal repeat results in haplotype for α_0 , α_4 , $\gamma_134.5$)

HF10 (naturally attenuated variant, Japan)

Summary of HSV1716 Pre-clinical Data

- Toxicology and biodistribution studies designed with and approved by FDA in support of IND (blinded and controlled animal study)
- LD₅₀ for murine intracranial injection > 10⁶ pfu
- Xenograft models – HSV1716 demonstrated efficacy in numerous tumor models including glioma, mesothelioma, melanoma, squamous cell carcinoma, ovarian, non-small cell lung cancer etc

Summary of Adult Data for HSV1716

Study	Design (Endpoint)	Patients
1	Adult high grade glioma: Dose escalation by intra-tumoral (ITu) injection (safety)	21
2	Adult high grade glioma: ITu injection ~1 week prior to surgical resection (safety and biological activity in resection tissue)	12
3	Adult high grade glioma: ITu injections into tumor bed immediately post resection (safety as adjunct to surgery)	12
4	Recurrent adult GBM: Repeat ITu injection into (safety of repeat injections)	2
5	Melanoma: ITu injection into nodules prior to removal (safety and biological activity, repeat injections)	5
6	Oral squamous cell carcinoma: ITu injection ~ 1 week prior to resection (safety and biological activity)	20
7	Mesothelioma: Single and multiple dose intrapleural administration (safety and biological activity)	2 (open)

Adult Data for HSV1716: Outcomes

- No virus-related toxicity reported at any dose or route of administration
- No virus shedding detected by buccal swab and urine sample
- Administration procedures well tolerated
- Evidence of HSV1716 replication in resection tissue obtained post administration
- Biopsy tumor tissue permissive for HSV1716 replication
- Notable individual case reports of prolonged survival
- Open study in UK administering higher dose of HSV1716 (10^7 iu) to the pleural cavity of mesothelioma patients

Mesothelioma Study with HSV1716

Patient Eligibility:

- Adults over 18 yrs of age with malignant pleural mesothelioma
- Subjects must have an indwelling pleural catheter for administration of HSV1716

Study design:

- Single and repeat dosing of 1×10^7 iu based on 3 +3 design, i.e. Three cohorts – (1) single dose (2) two doses and (3) four doses, each one week apart with option for expansion cohort at applicable dosing frequency

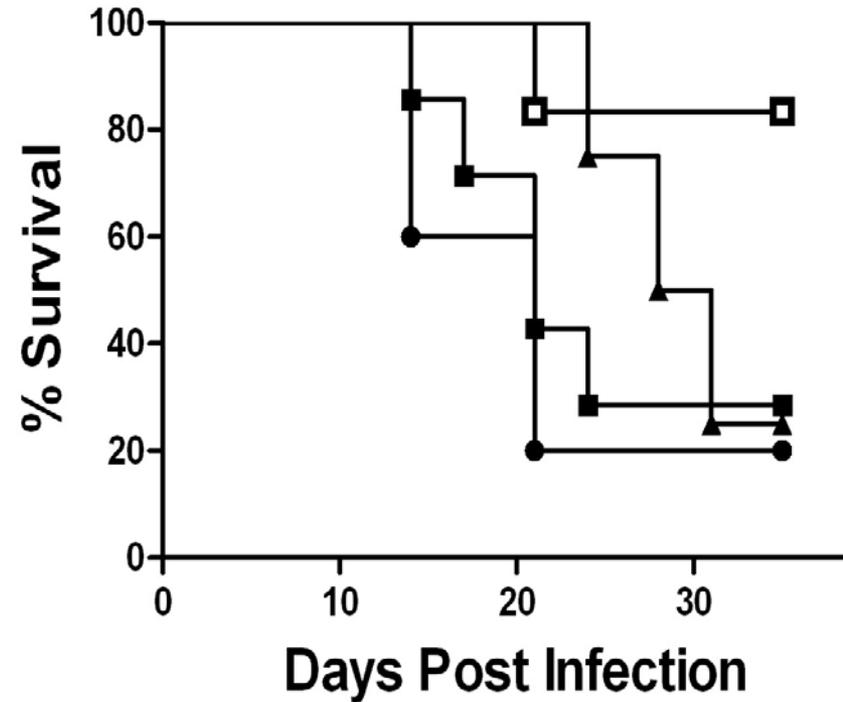
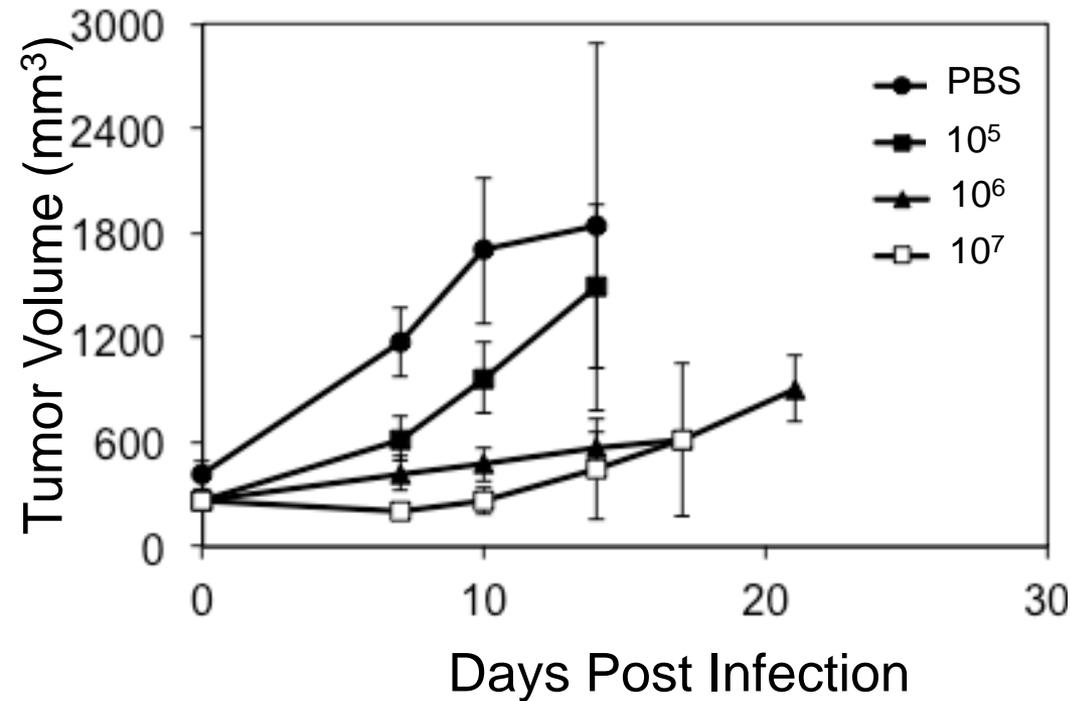
Study Status:

- N=2 patients treated in cohort (1)
- No DLTs or SAE's reported.

Outcome:

- CT scans in both patients have revealed progressive disease following single dose administration.

Intratumoral HSV1716 in A673 Ewing Sarcoma Flank Xenograft Model



A Phase I Dose Escalation Study of Intratumoral or Intravenous Herpes Simplex Virus-1 Mutant HSV1716 in Patients with Non-Central Nervous System Solid Tumors

Sponsor: Timothy P. Cripe, M.D., Ph.D.

Original Principal Investigator: Timothy P. Cripe, M.D., Ph.D.

Current Principal Investigator: James Geller, M.D.

Study Objectives

- **Primary**
 - Determine safety and dose limiting toxicities
- **Secondary**
 - Monitor antiviral immune response, viremia, virus shedding
 - Define antitumor activity

Study Design - Original

- Treatment plan:
 - PART 1: A single intratumoral dose
 - PART 2: Up to 3 additional doses, ≥ 28 days apart
 - ❖ Optional biopsy to detect virus in tissue
- Doses :
 - Level 1: 1×10^5 iu (1mL)
 - ❖ 3 subjects, any site
 - Level 2: 2×10^6 iu (1mL)
 - ❖ 3 subjects in each of 3 site classifications
 - ✧ superficial, deep, intra peritoneal
- Outcomes:
 - Safety: toxicity, virus shedding, antiviral response
 - Efficacy: Tumor response

Study Status

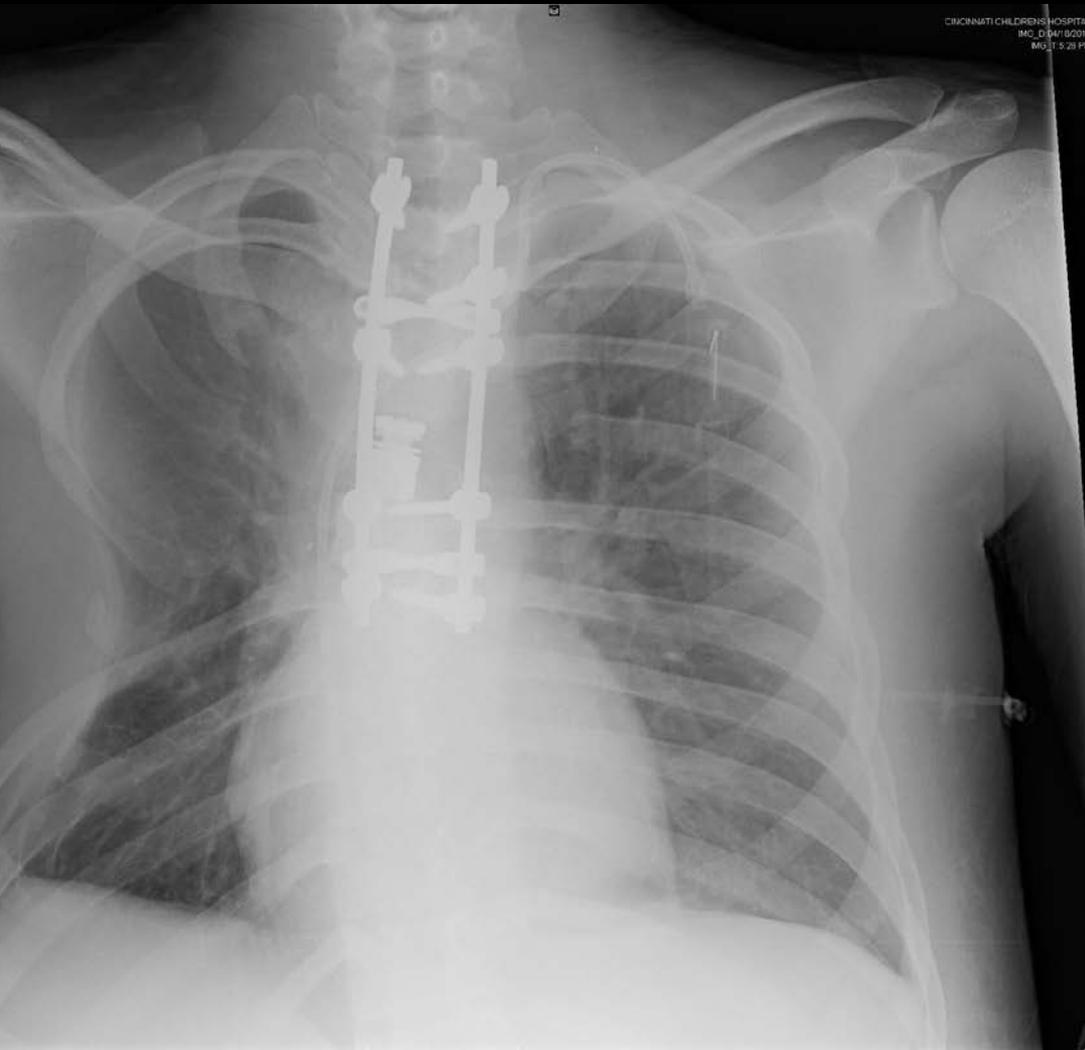
Intratumoral injection:

- 5 patients to date
- 3 enrolled at dose level 1 (1×10^5 IU)
- 2 patients enrolled at dose level 2 (2×10^6 IU)
- Diagnosis: Rhabdomyosarcoma, Ewing sarcoma, paraspinal MPNST, osteosarcoma, clival chordoma
- No treatment related serious adverse events or major toxicities

HSV04

- Age: 19 year old male
- Diagnosis: Recurrent osteosarcoma
- Location: Paraspinal
- Prior treatment:
 - Multiple surgeries
 - Multiagent chemotherapy regimens (Dox/CDDP/HDMTX, Gem/Doc, I/E)
 - Targeted agents (IMC-A12/Temsirolimus)
- Family history:
 - p53 germline mutation (Li-Fraumeni syndrome)
 - Father (deceased) with leukemia
 - Sister with lymphoma
 - Brother (deceased) with osteosarcoma
- Condition:
 - Paraplegia from tumor extension into spinal canal
 - Tubulopathy with chronic wasting of electrolytes, indwelling Foley
 - Chronic pain in back and left arm
 - Recurrent skin breakdown on legs

Se: 3
P: 53.9



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Safety Summary: Adverse Events

- All subjects have been assessed for Dose Limiting Toxicities through the Day 28 visit
 - No Dose Limiting Toxicities have been observed.
- AEs at least *possibly* related to HSV1716 have been mild (\leq grade 2) and transient.
- All HSV culture results have been negative.
- There have been some instances of low-positive PCR results (HSV03, HSV04) without clinical evidence of HSV infection.

Safety Summary: HSV Serology

	HSV immune status (Pos = ≥ 1.10 ; Neg = ≤ 0.89)			
	IgG (iu)		IgM (iu)	
	Baseline	D28	Baseline	D28
HSV05	Neg (<0.08)	Neg (0.03)	Neg (0.18)	Neg (not given)
HSV04	Neg (0.55)	Pos (6.40)	Neg (0.09)	Pos (3.98)
HSV03	Neg (0.17)	Pos (1.77)	Neg (0.68)	Neg (0.75)
HSV02	Pos (22.4)	Pos (7.90)	Neg (0.20)	Neg (0.11)
HSV01	Neg (0.17)	Pos (3.11)	Neg (0.36)	Pos (1.54)

Efficacy Summary

- Five subjects have been assessed for initial evidence of efficacy.
- The first four subjects were determined to have progressive disease.
- The fifth subject was determined to have stable disease at the injected site on Day 14.
 - However, on Day 28, the subject was determined to have progressive disease at the injected site.
 - Although eligible for PART 2, this subject did not receive additional injections.

Study Conduct Summary: Adverse Events

- Total adverse events: 284
 - 21 associated with a SAE report
- The top categories with the highest numbers of adverse events are:
 - Metabolic/Laboratory: 84 (30%)
 - Blood/Bone Marrow: 52 (18%)
 - Pain: 32 (11%)
 - Gastrointestinal: 31 (11%)
- 23 *unexpected* adverse events
 - None were possibly, probably, or definitely related to HSV1716

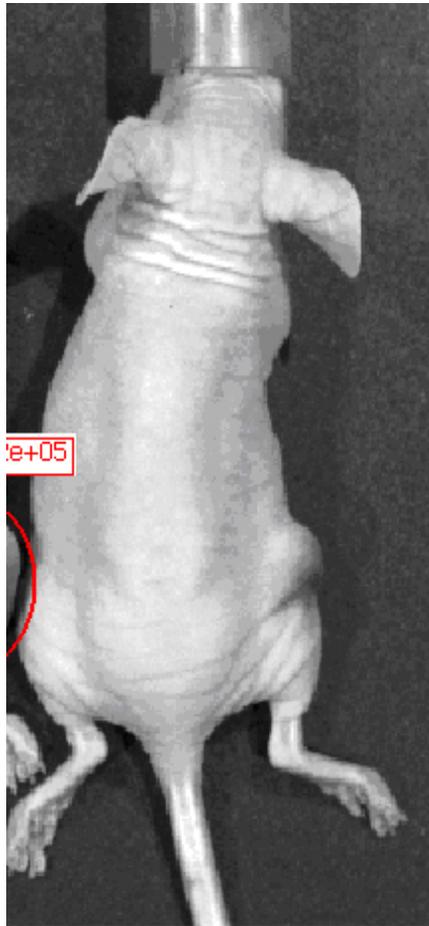
Study Limitations and Plans

- Limitations:
 - Slow enrollment
 - 23 screened, only 5 enrolled
 - ❖ **Preference for studies with systemic treatment**
 - ❖ Rapid disease progression
 - ❖ Age (too young)
 - Low efficacy, likely due in part to low doses
- Recent amendments
 - Add higher intratumoral dose level
 - Add intravenous cohort
- Systemic administration: preclinical data
 - IV Toxicology study
 - IV Biodistribution study
 - IV Efficacy study

HSV1716 IV Toxicology Study

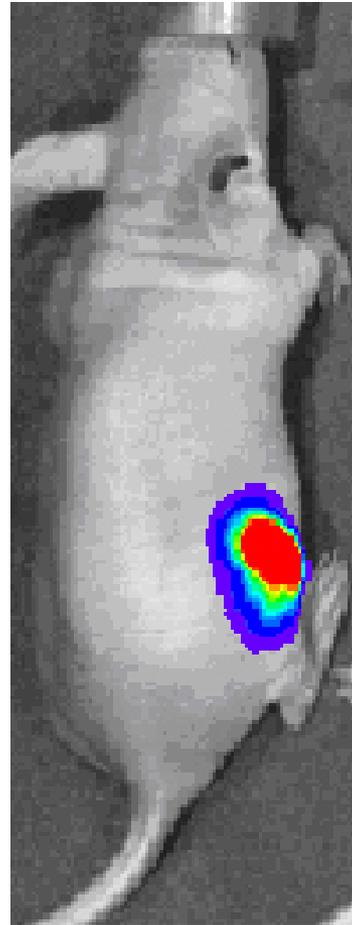
- 66 animals given 1.8×10^5 iu ($\sim 7 \times 10^6$ iu/kg)
 - 300-fold above proposed highest trial dose
- 100% survival to respective timepoints
- Observations, weights, chemistries, CBCs, histopathology of 21 organs from each mouse
- Inconsistent changes also observed in mice given excipient (tail necrosis/abscess, elevated bilirubin, epicardial calcifications)

HSV1716 IV Biodistribution Study

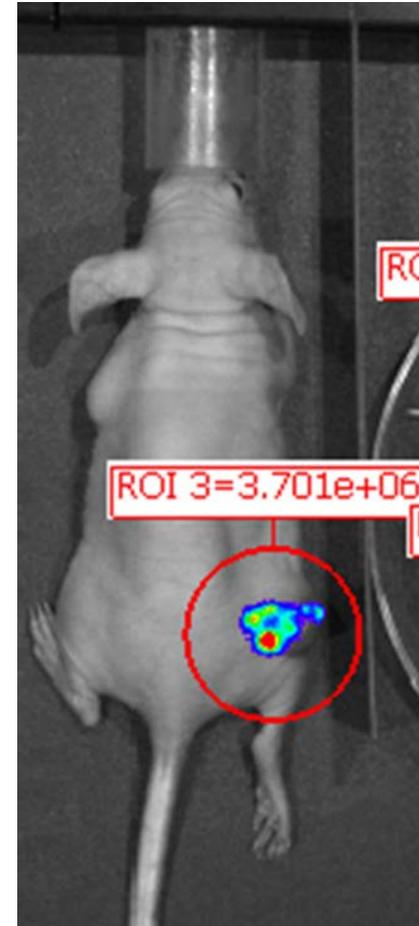


Subcutaneous
HuH7 xenograft

1x10⁷ iu HSV1716luc
IV administration



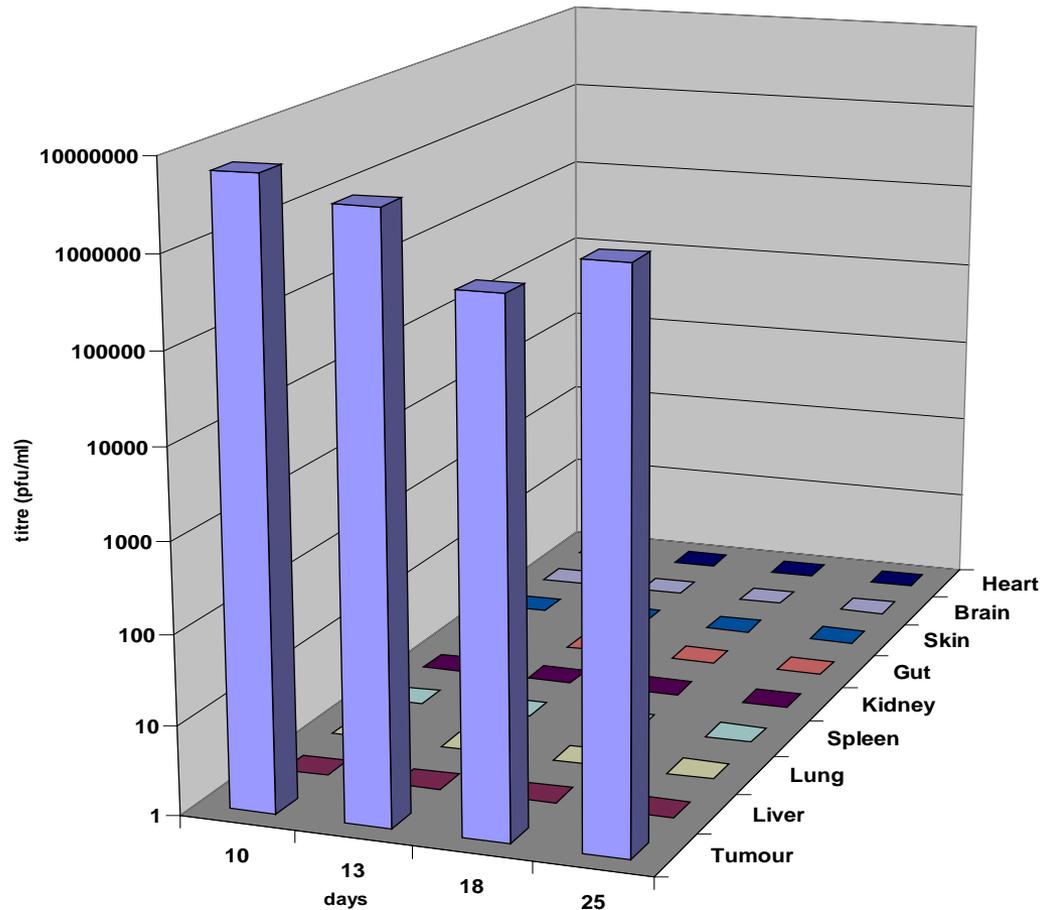
72 hrs after
injection



21 days after
injection

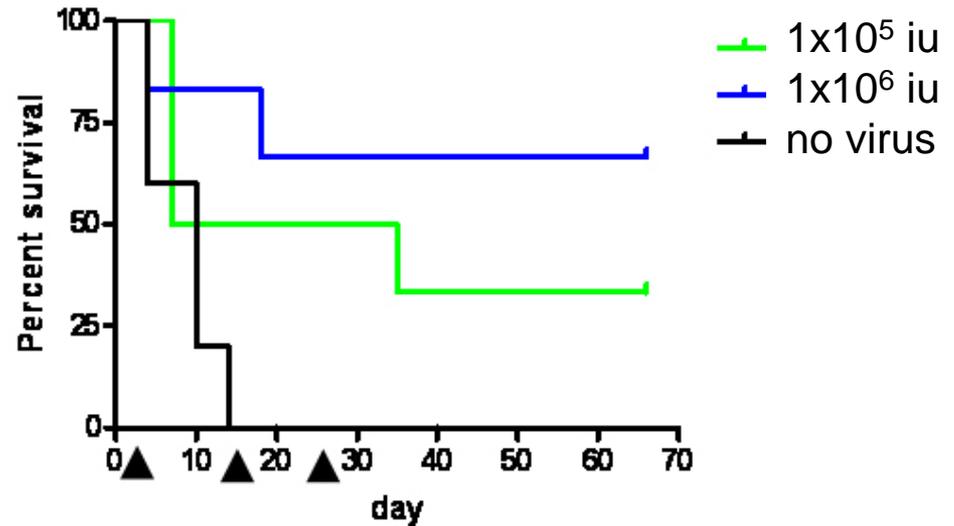
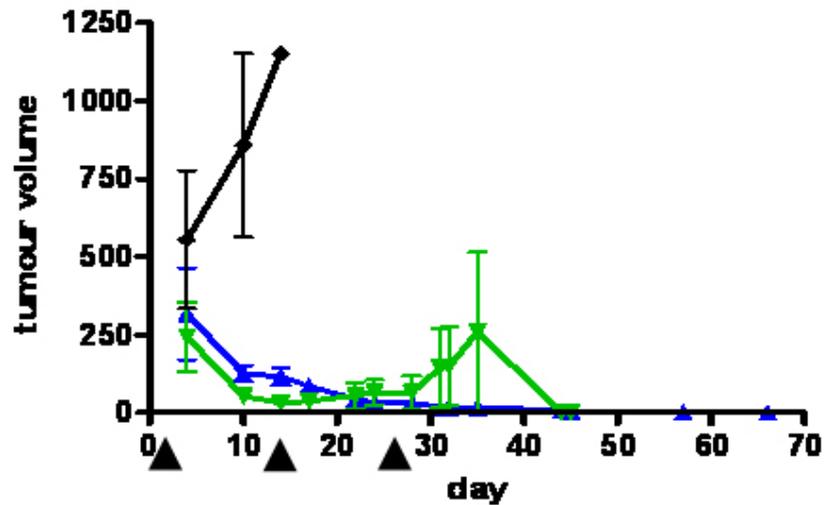
- IV HSV1716luc localizes exclusively to tumour xenografts.

1x10⁷ iu HSV1716 administered by tail vein injection on days 1 and 4



- Day 10 n=2, day 13 n=1, day 18 n=1, day 25 n=3
- HSV1716 detected only in xenografts
- No HSV1716 was detected in liver, lung, heart, spleen, kidney, skin, gut or brain.²⁷

HSV1716 IV Preclinical Efficacy



- HSV1716 administered by IV on days 1 and 14 and 29
- The difference in growth for untreated vs treated is highly significant by ANOVA ($p < 0.0001$)
- Enhanced survival in both groups treated with HSV1716 ($p = 0.0157$)
- On day 66 when the experiment was stopped:-
 - 2/6 mice treated with 1×10^5 iu were cured
 - 4/6 mice treated with 1×10^6 iu were cured

Study Design – Current (v12.2)

- Treatment plan:
 - PART 1: A single intratumoral or intravenous dose
 - PART 2: Up to 3 additional doses, ≥ 28 days apart
 - ❖ If intratumoral, optional biopsy to detect virus in tissue
- Doses :
 - Intratumoral**
 - Level 1: 1×10^5 iu (1mL)
 - Level 2: 2×10^6 iu (1mL)
 - Level 3: 1×10^7 iu (1mL) – (proposed in amendment v13)
 - Intravenous**
 - Level 1: 5×10^4 iu/kg (2×10^6 iu for 40 kg person)
 - Level 2: 2.5×10^5 iu/kg (1×10^7 iu for 40 kg person)
 - Level 3: 1.25×10^6 iu/kg (5×10^7 iu for 40 kg person) – (deleted in v13 due to inadequate supply)
- Outcomes:
 - Safety: toxicity, virus shedding, antiviral response
 - Efficacy: Tumor response

IV Cohort Safeguards

- First 3 patients >18 yo
- 28 day observation period between first 3 patients
- IRB review of data prior to enrolling younger patients
- Younger patients restricted to ≥ 7 yo
- No 2nd dose for any patient until 3 patients have received single dose and completed DLT observation period

Amendment Status

- Version 12.2 - Intratumoral and IV open for accrual at Cincinnati Children's
 - IBC - approved
 - IRB - approved
 - FDA CBER
 - ❖ Approved for single IV dose
 - ❖ Hold on multiple IV doses pending further review of first three patients administered single IV dose
 - RAC – update today
- Version 13 – Revised dose levels
 - On file with IND
 - Under submission at Nationwide Children's and Cincinnati Children's

Summary

- Numerous studies have demonstrated safety of various intravenous oncolytic viruses
- Adult studies of intratumoral HSV1716 show safety
 - Single and multiple dosing
 - Doses up to 10^7 iu
- Adult studies with other herpes simplex viruses given intravascularly show safety
 - Intra-hepatic artery of NV1020 (up to 1×10^8 pfu, weekly x 4)
 - Intra-hepatic artery of rRp450 (ongoing, doses $>10^9$ pfu)
- Preclinical IV studies of HSV1716 show safety and efficacy
- Pediatric/young adult phase I study
 - Results to date show safety of intratumoral injection but few hints of efficacy – doses being tested are quite low
 - Accrual is poor as most patients have metastatic disease

Acknowledgements

- Preclinical Studies
 - NCI
 - Alex's Lemonade Stand
 - Cancer Free Kids
 - Katie Linz Foundation
 - Teeoffagainstcancer.org
- Clinical Trial
 - Solving Kids Cancer
 - Virttu Biologics, Ltd.
 - FDA Orphan Drug Grant Program (intratumoral cohort)