



SITC 2018

NOVEMBER 7-11
WASHINGTON, D.C.

Walter E. Washington
Convention Center



Society for Immunotherapy of Cancer

Characterization of anti-tumor immune responses and effects on survival of neoadjuvant oncolytic virotherapy in spontaneous osteosarcoma

Naik S,¹ Makielski KM,² Henson MS,² Stuebner KM,² Tabaran AF,² Cornax I,² O'Sullivan MG,² Eckert A,² Groschen D,² Mills L,² Scott MC,² Sarver AL,² Farrar M,² Russell SJ,¹ Modiano JF²

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Society for Immunotherapy of Cancer

#SITC2018

Presenter Disclosure Information

KELLY MAKIELSKI

The following relationships exist related to this presentation:

No Relationships to Disclose

There will not be discussion about the use of products for non-FDA approved indications in this presentation

Unmet clinical need for new therapies that target metastatic progression in osteosarcoma

- The most common primary bone cancer in children and young adults¹
- Current standard of care includes surgery and chemotherapy
- Over 40% of patients have metastatic progression following standard of care²
- Rarity of this disease limits clinical testing

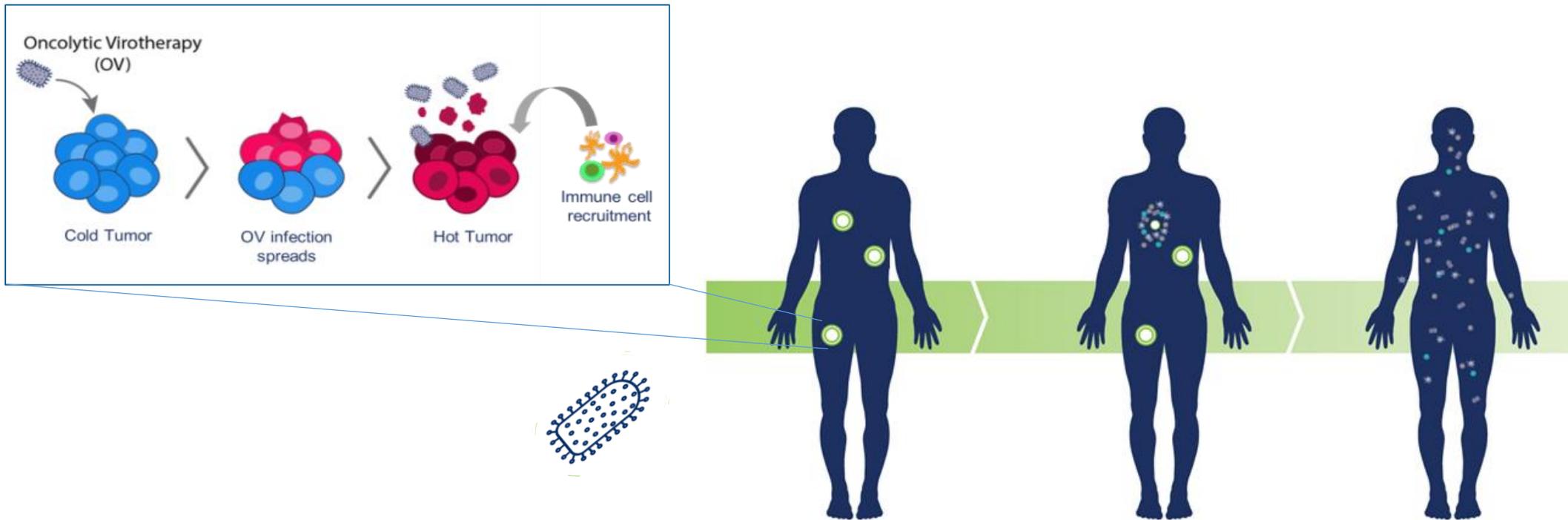
1. Marina, NM et. al. *The Lancet Oncology*; 17 (10): October 1, 2016

2. Allison, DC et. al. *Sarcoma*; 2012

Testing novel therapies in naturally occurring osteosarcomas in pet dogs

- Common canine malignancy occurring in the limbs of large dog breeds
- Standard of care is surgery & chemotherapy
- Similar histology and clinical disease course as human osteosarcoma
- Death largely due to pulmonary metastases
- Compressed progression time - median survival is ~1 year

Oncolytic virus therapy: selectively kills tumor cells and promotes intratumoral immune infiltration



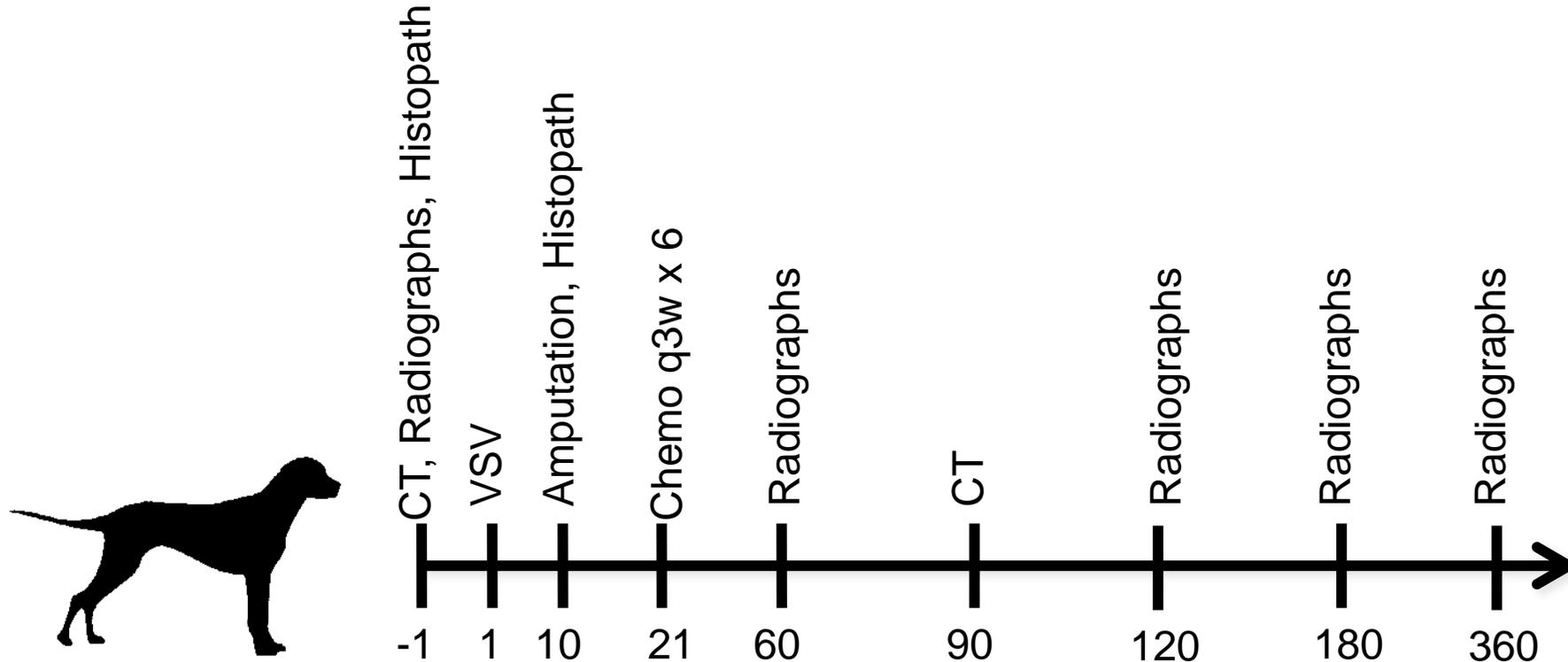
Vesicular stomatitis virus has been engineered for safe intravenous therapy of disseminated/metastatic cancer ¹



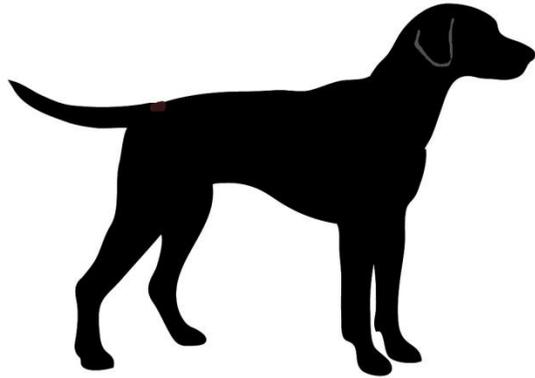
VSV	IFN β	NIS
<ul style="list-style-type: none"> • Potent systemic anticancer agent • Fast replication and killing • Increases inflammation within the tumor 	<ul style="list-style-type: none"> • Anti-proliferative • Anti-angiogenic • Targets virus tropism • Amplifies adaptive immunity 	<ul style="list-style-type: none"> • Reporter gene for PET/SPECT imaging of virus spread • Allows radioisotope boosting of potency (radiovirotherapy)

1. Naik et. al. *Leukemia*; 26 (8): August 2012

VIGOR: VSV immunotherapy & genomics for osteosarcoma research



VIGOR: correlative studies and immune monitoring



GOALS

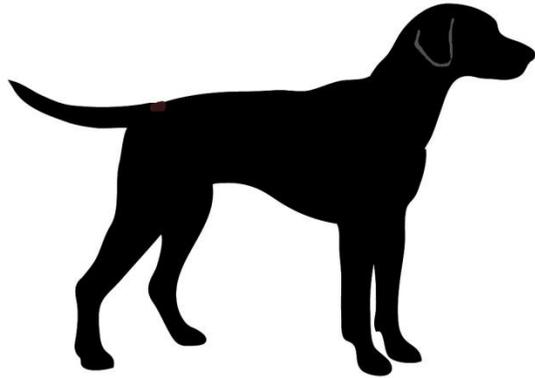
- Determine tolerability

TOLERABILITY

(CBC, Chem, COAG)

- Intravenous VSV-IFN-NIS therapy is well tolerated

VIGOR: correlative studies and immune monitoring



GOALS

- Determine tolerability
- Determine biosafety

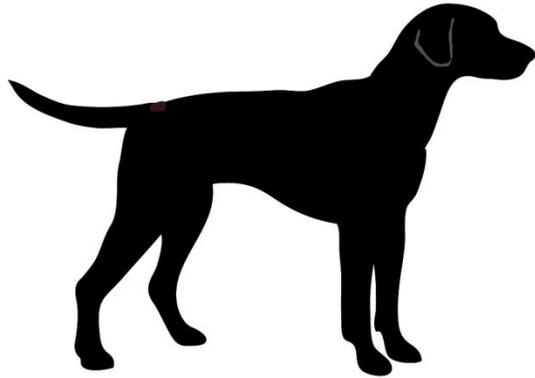
TOLERABILITY

(CBC, Chem, COAG)

- Intravenous VSV-IFN-NIS therapy is well tolerated

PK/SHEDDING

VIGOR: correlative studies and immune monitoring



GOALS

- Determine tolerability
- Determine biosafety
- Determine efficacy

TOLERABILITY

(CBC, Chem, COAG)

- Intravenous VSV-IFN-NIS therapy is well tolerated

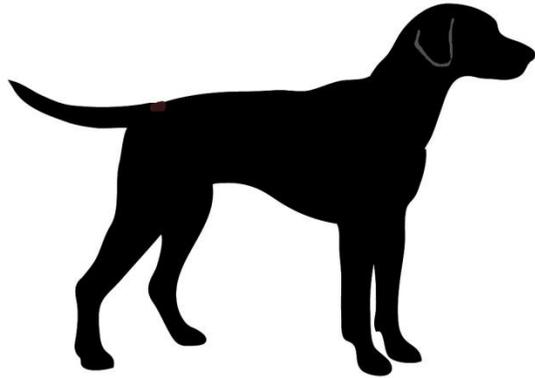
PK/SHEDDING

CLINICAL OUTCOME

(PFI, OS)

- Analysis ongoing

VIGOR: correlative studies and immune monitoring



GOALS

- Determine tolerability
- Determine biosafety
- Determine efficacy
- Determine effect on anti-tumor immunity of neoadjuvant IV VSV-IFN β -NIS therapy

TOLERABILITY

(CBC, Chem, COAG)

- Intravenous VSV-IFN-NIS therapy is well tolerated

CLINICAL OUTCOME

(PFI, OS)

- Analysis ongoing

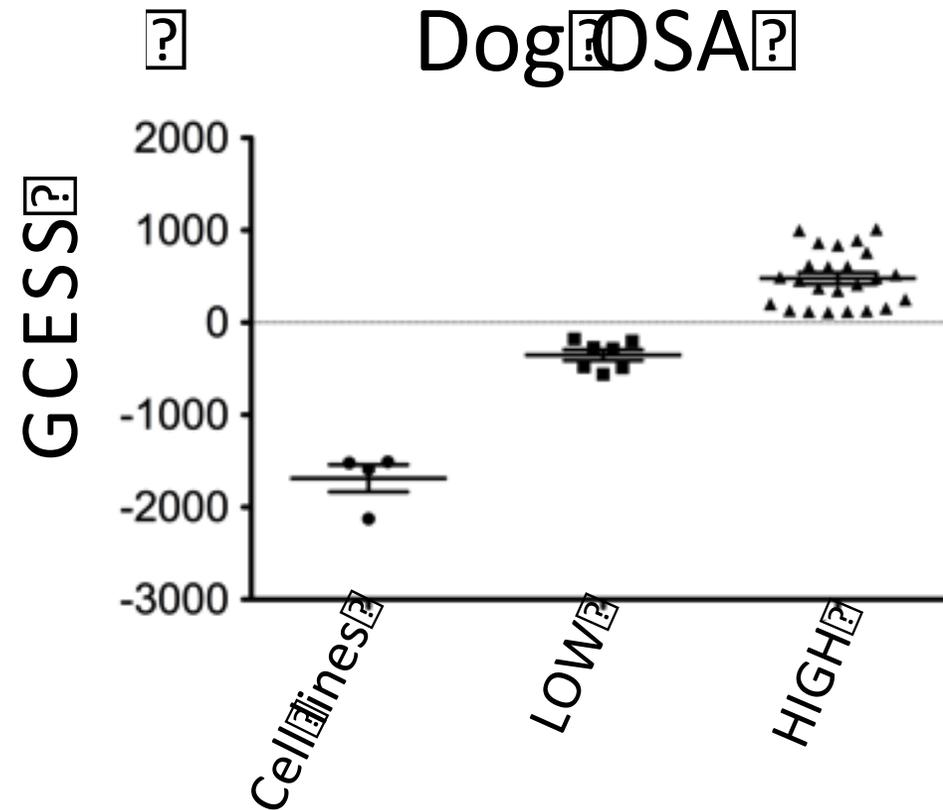
PK/SHEDDING

HISTOPATHOLOGY

GCESS

CLONALITY

GCESS analysis



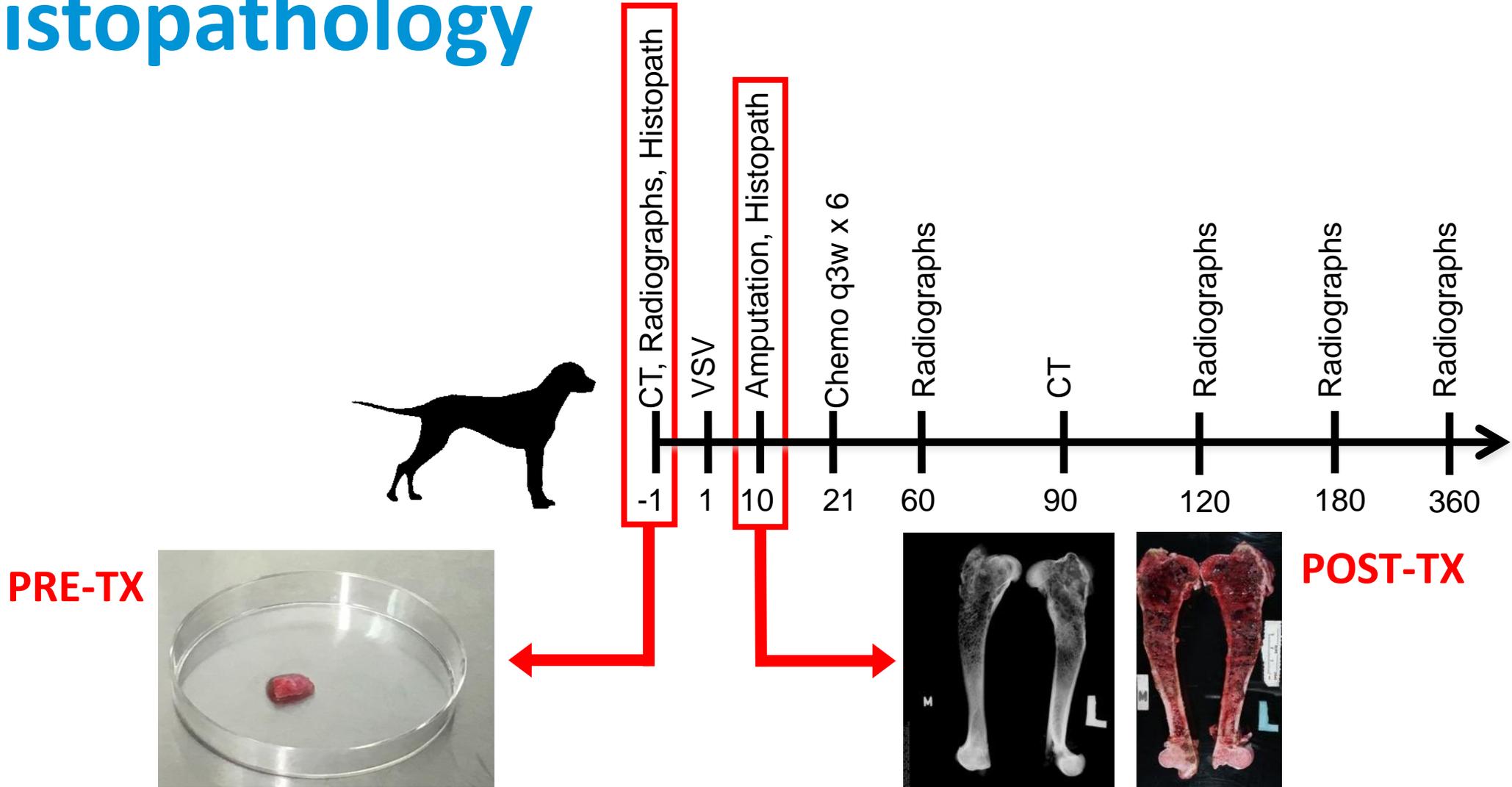
Inclusion criteria

- **Appendicular osteosarcoma**
- **Body weight > 20kg**
- **No pathologic fracture or metastasis**
- **No significant comorbidities**

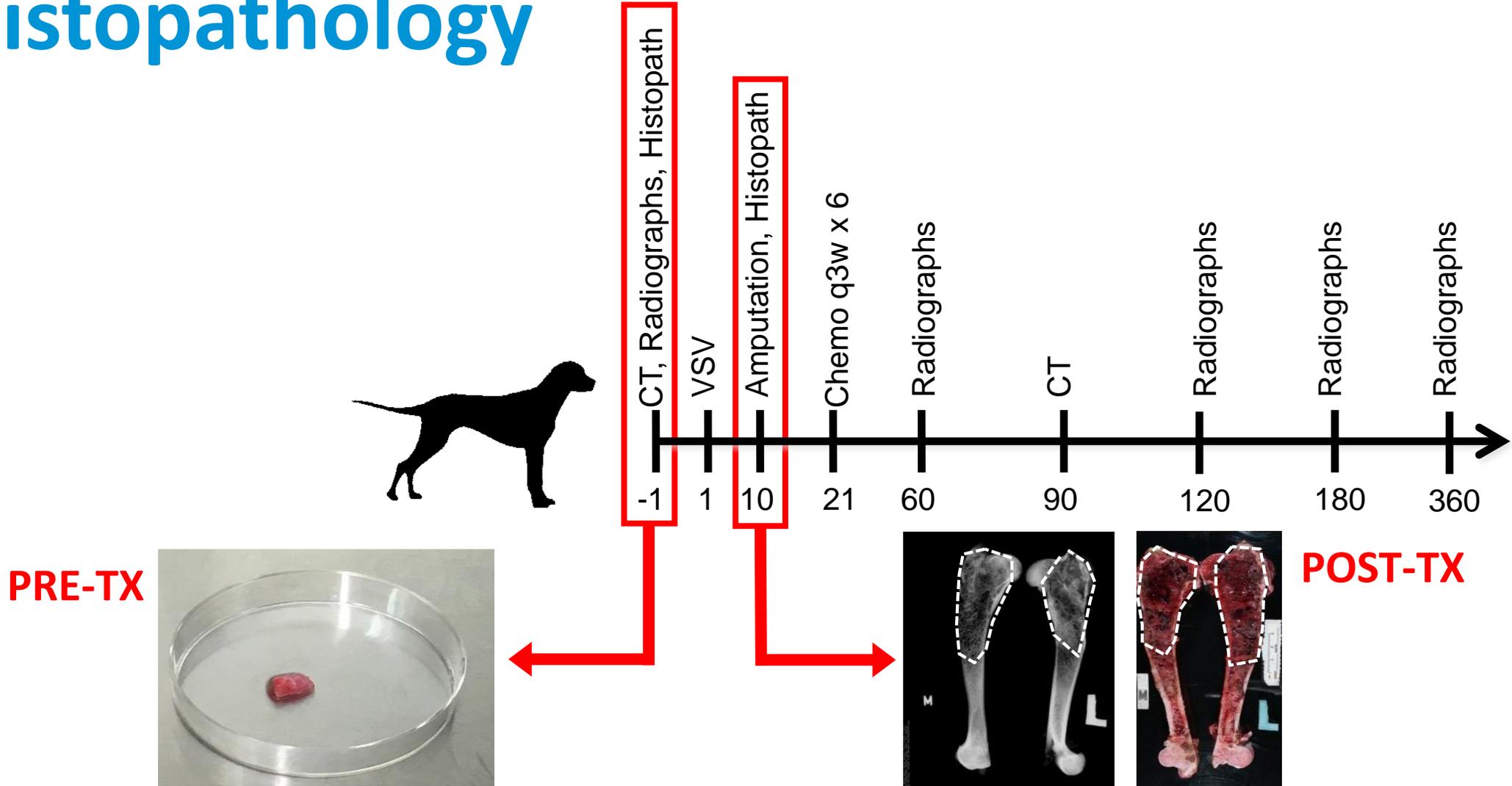
Enrollment & safety

- **Current enrollment at 27 dogs**
- **Virus detected in PBMCs 1h post-administration**
- **No detectable shedding in biologic fluids**
- **Mild self-limiting changes in body temperature**

Histopathology

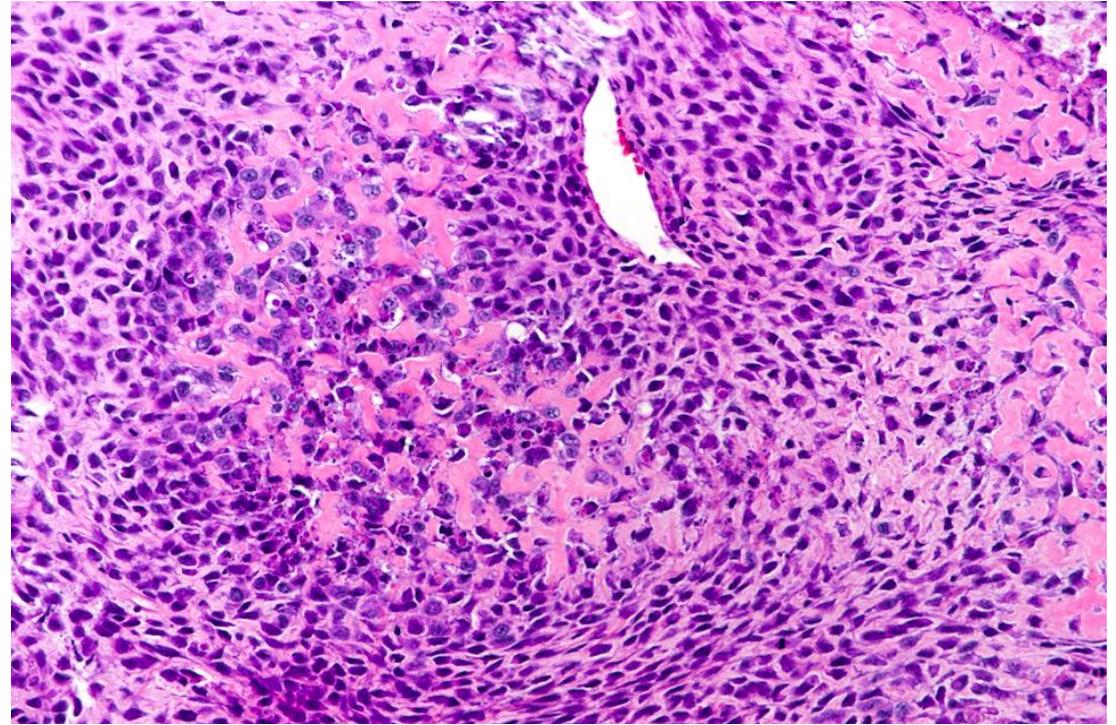
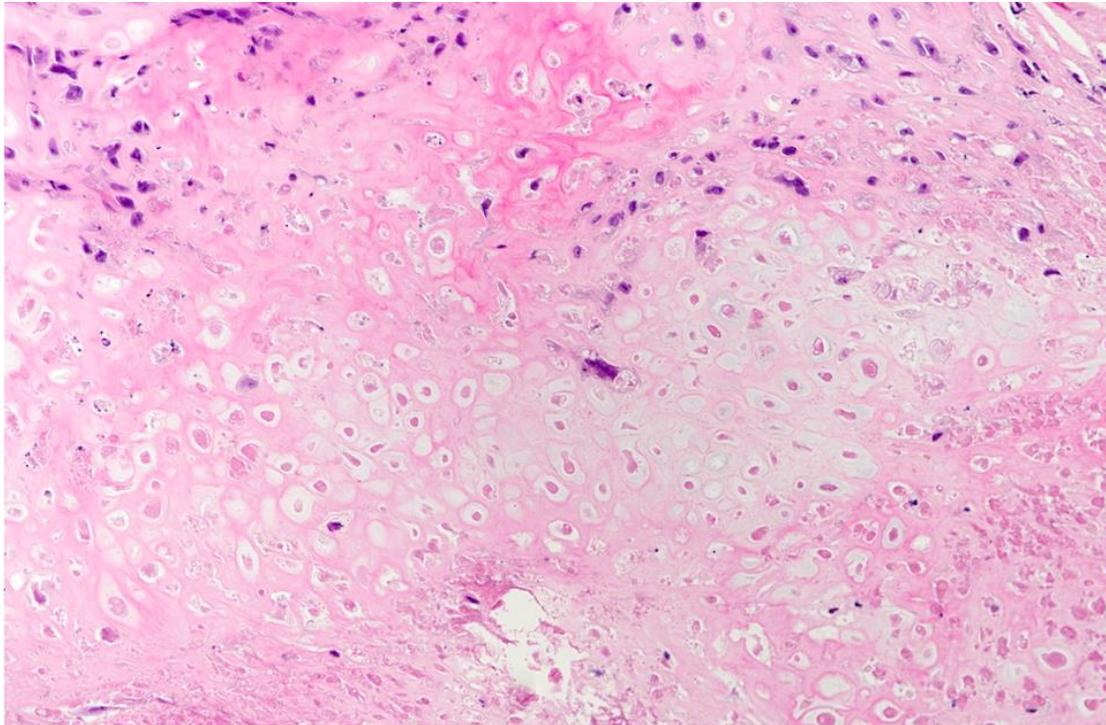


Histopathology



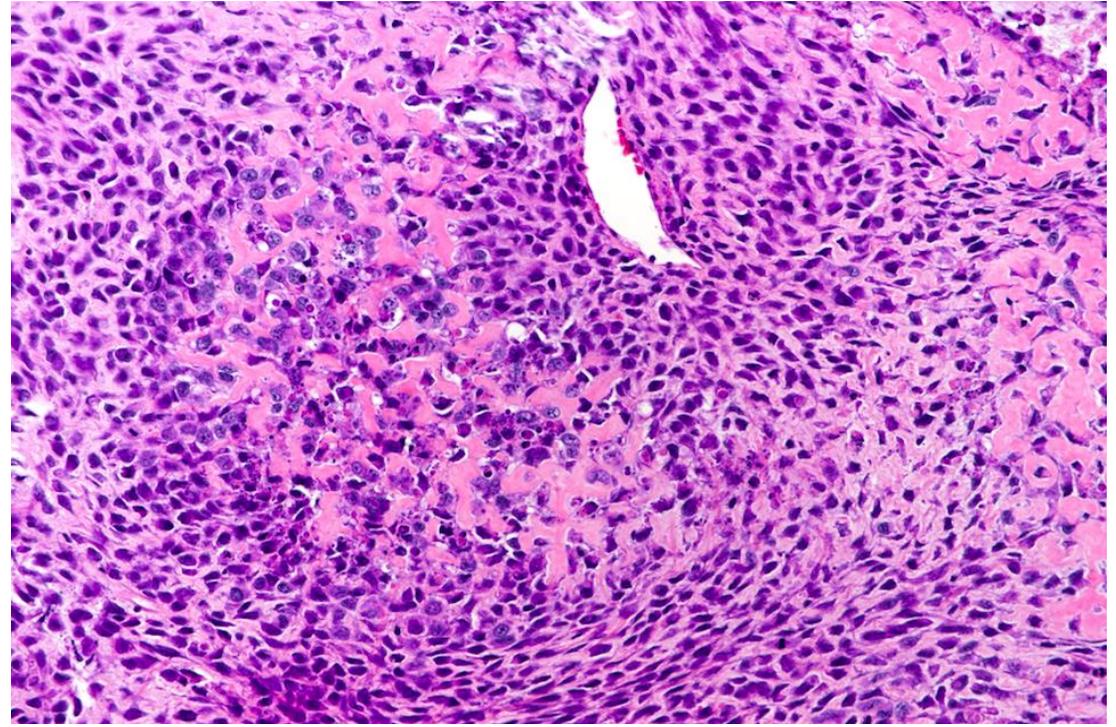
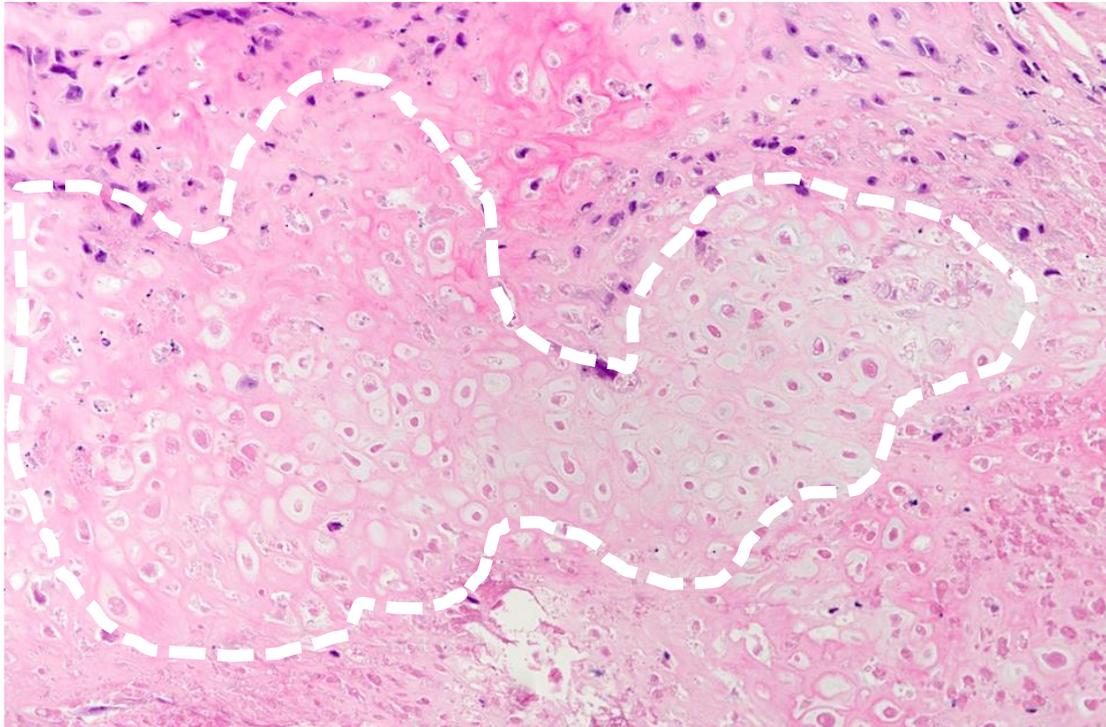
Focal necrosis observed in tumors of VSV treated dogs (different from ischemic necrosis normally observed in osteosarcoma surgical specimens)

H&E Stain; 20x



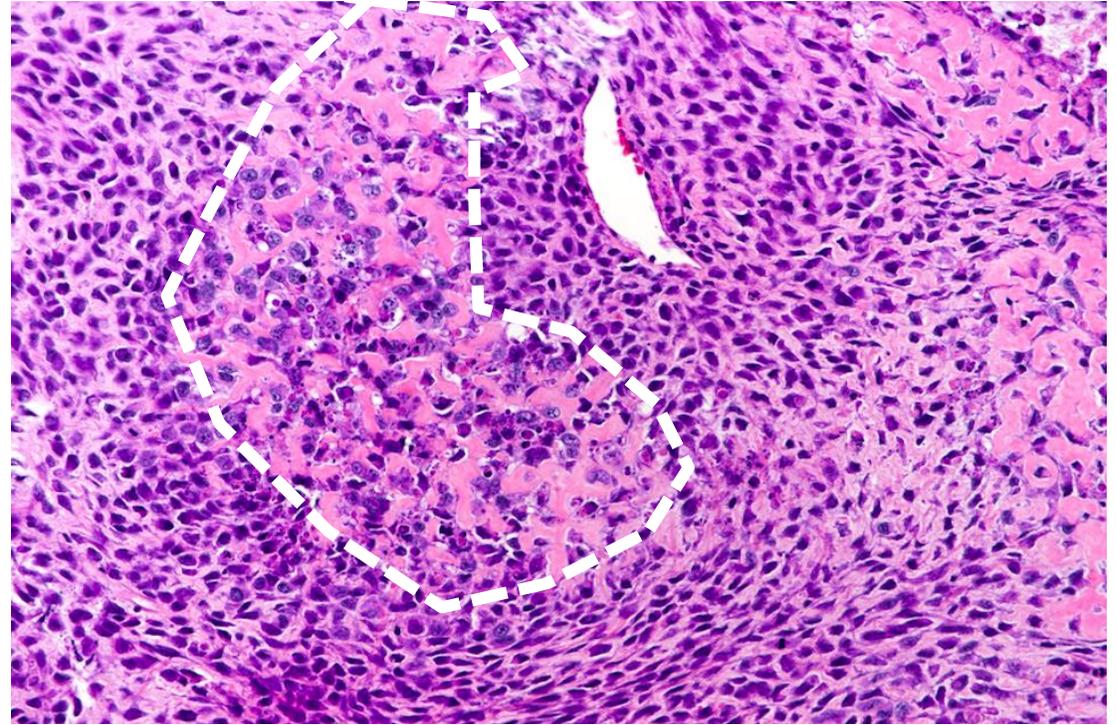
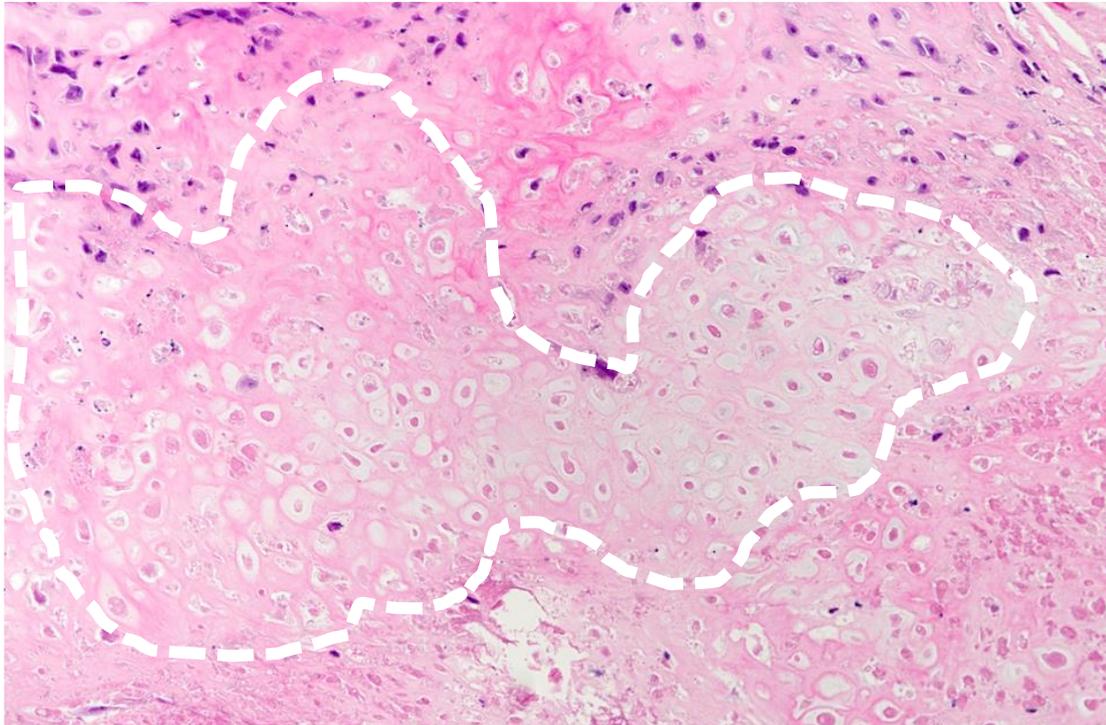
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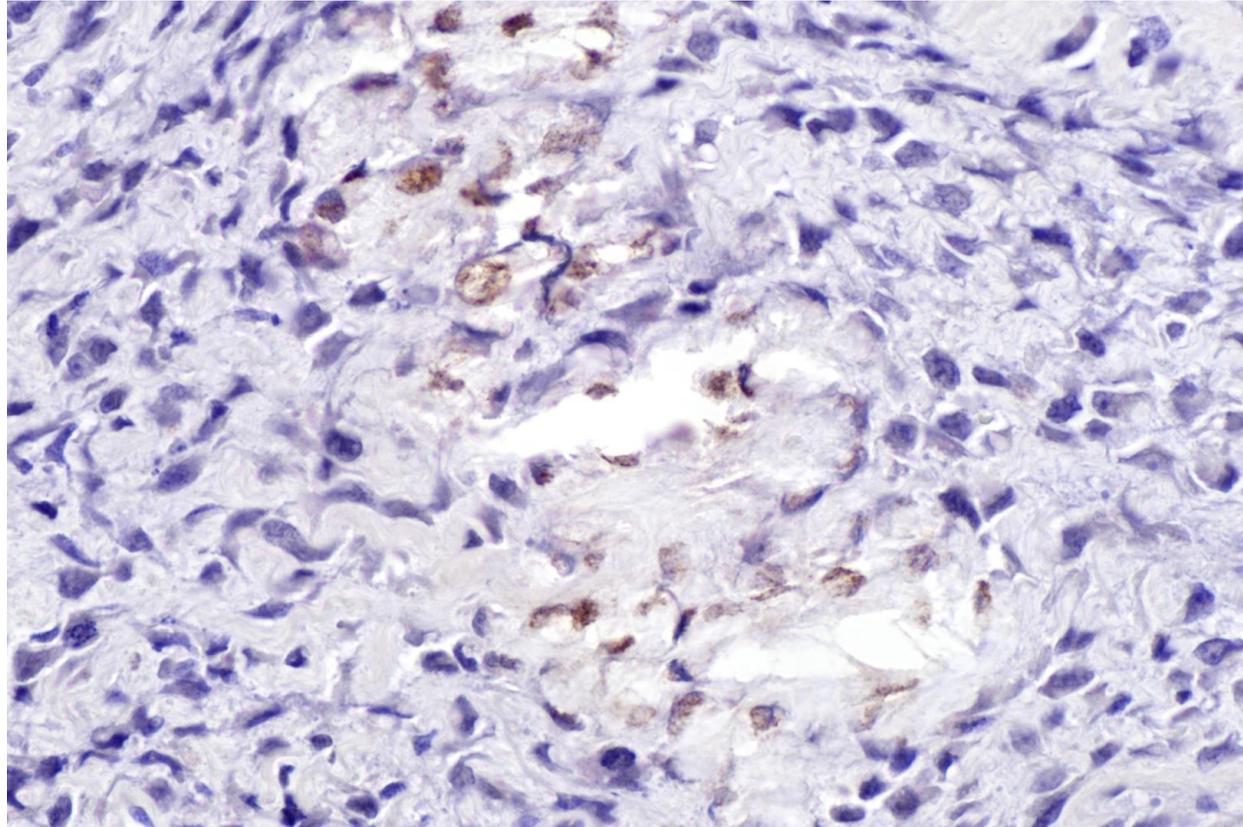


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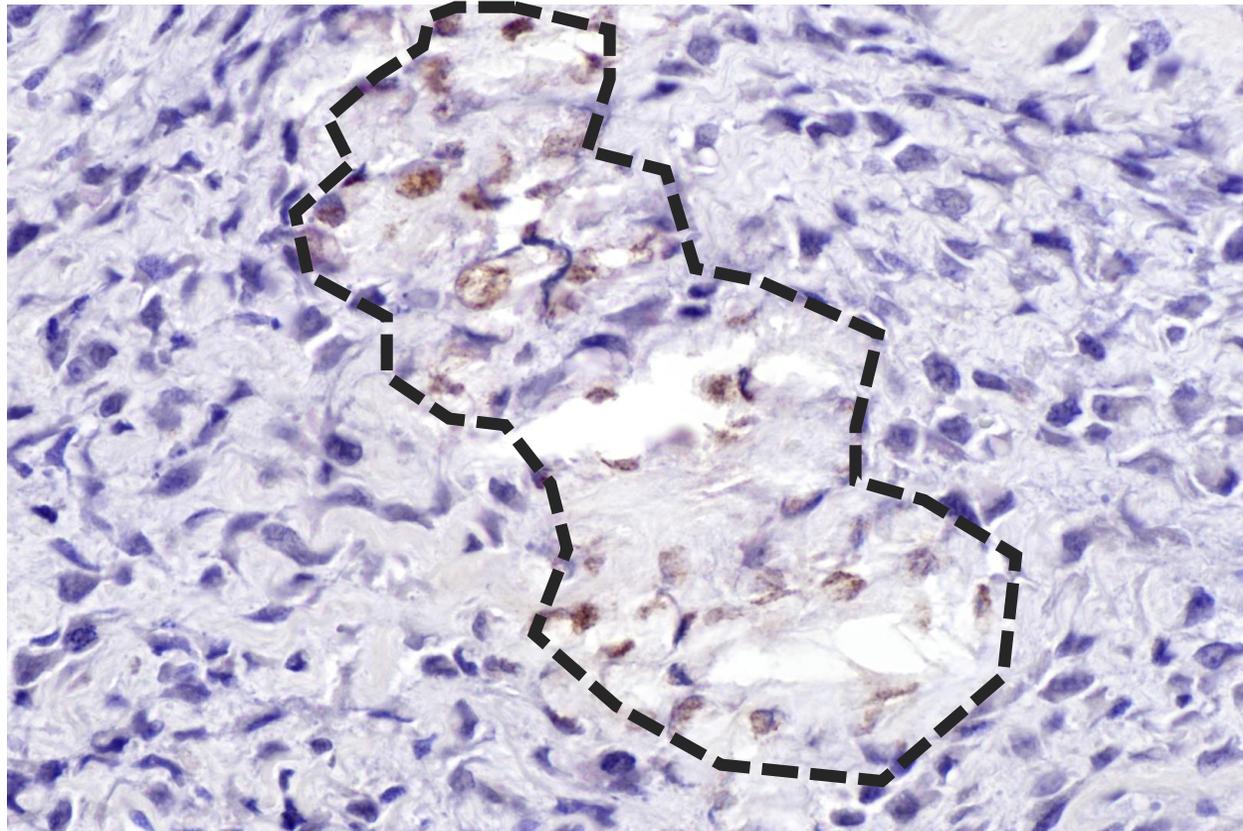


Histopathology: IHC with anti-VSV antibody



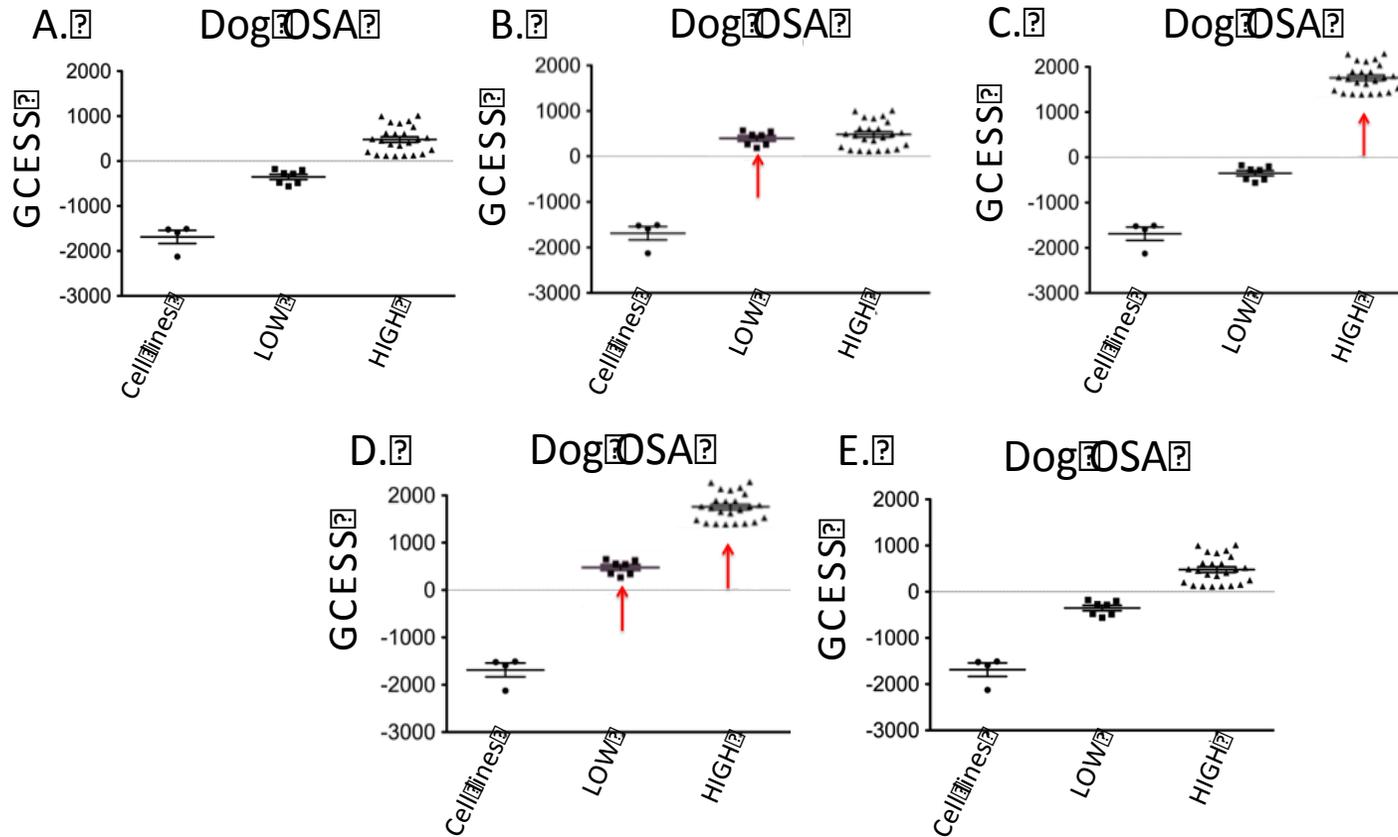
IHC; 40x

Histopathology: IHC with anti-VSV antibody

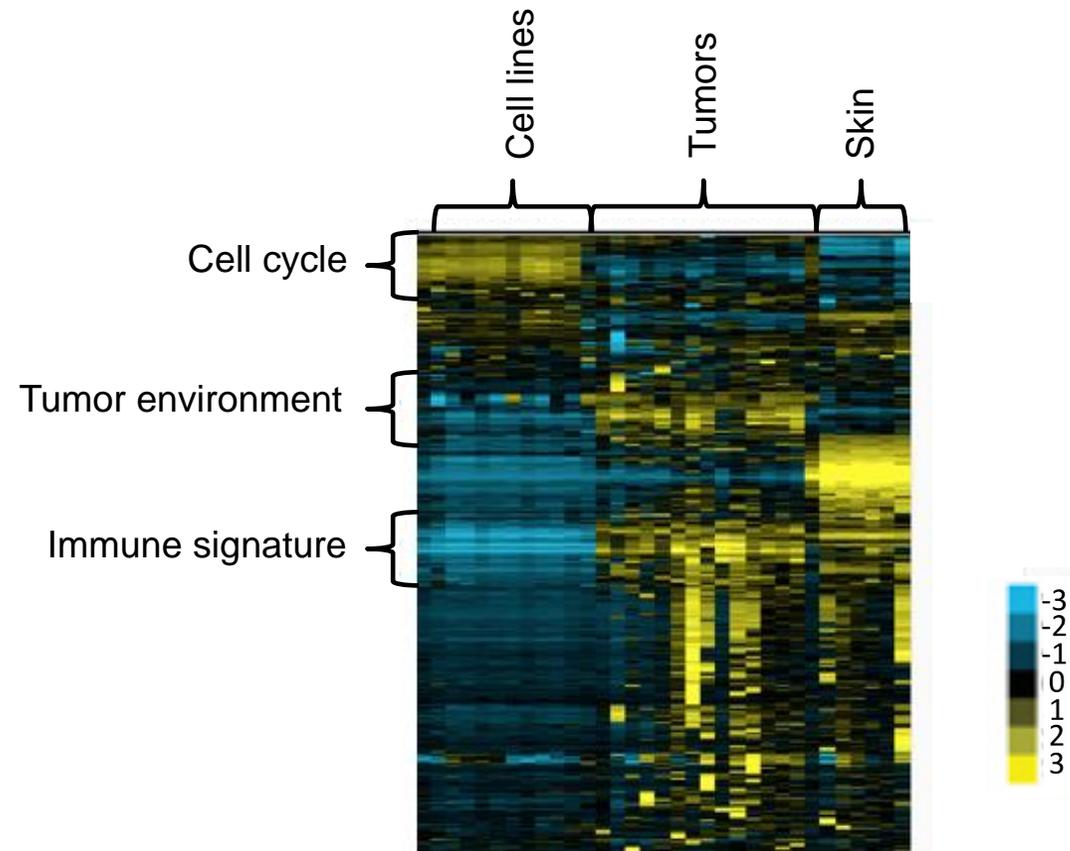


IHC; 40x

Potential outcomes



RNA sequencing identifies gene signatures associated with cell cycle and immune cell infiltration

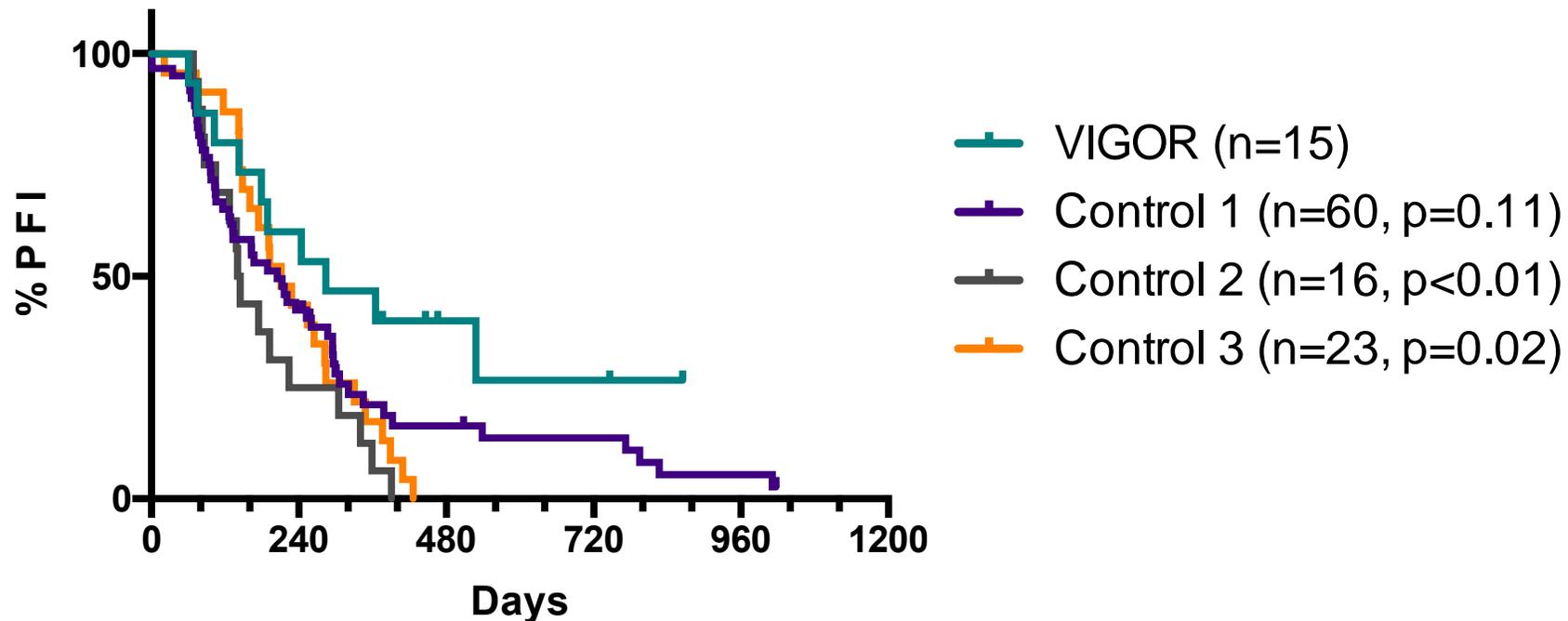


Clonality

- **Methodology to evaluate clonal expansion adapted for large scale NGS**
- **Confirmed amplification of IgH & TCR**
- **Established UMIs for bias correction**
- **Sequencing of samples ongoing**

Preliminary evidence that VSV improves prognosis over SOC when compared with historical controls

Progression Free Interval



Conclusions

- **Oncolytic VSV has an excellent safety profile**
- **Preliminary evidence of biologic activity**
- **Canine clinical trials provide an opportunity for investigating anti-tumor immunity**

Acknowledgements & funding

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UNIVERSITY OF MINNESOTA

Animal Cancer Care & Research Program





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Clinical data

Enrolled Dogs (n=26)		
Breed	Golden Retriever	n=4
	Labrador Retriever	n=3
	Mastiff	n=2
	Other purebred	n=10
	Mixed breed	n=7
Tumor location	<u>Thoracic limb</u>	<u>n=19</u>
	Humerus	n=10
	Radius	n=8
	Ulna	n=1
	<u>Pelvic limb</u>	<u>n=7</u>
	Femur	n=2
	Tibia	n=5
Sex	Spayed female	n=16
	Castrated male	n=10
Age (years)	Mean	7.3
	Median	8
	Range	2–12.5
Body weight (kg)	Mean	38.8
	Median	33.8
	Range	20.2–81.6