The NCI Comparative Oncology Program: Clinical Trials in Pet Dogs with Cancer and Insight for Humans

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NIH NATIONAL CANCER INSTITUTE

14th Joint Meeting of the Board of Scientific Advisors & National Cancer Advisory Board
December 3, 2019

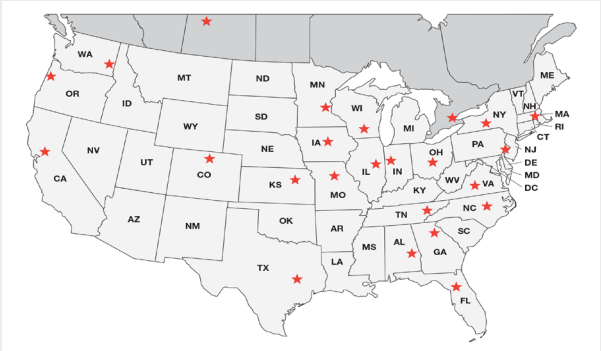
The State of Comparative Oncology in North America

Intramural + Extramural NCI – Comparative Oncology Program Focus on Cancer Drug Development and Translational Tumor Biology

The NCI Comparative Oncology Trials Consortium

Integration of Comparative Oncology within the Cooperative Group Structures

(Children's Oncology Group; NCI-CTEP, NeXT)



Comparative Cancer Genomics
Breen Lab – NCSU
TGen
Broad Institute
Ostrander Laboratory- NIH/NHGRI

Study of gene-environment and cancer-associated risk factors

Increasing support from Pharma to conduct early phase studies with novel cancer therapeutics

NIH or other National Funding/Philanthropy for Comparative Oncology Research

10 Veterinary Colleges with formal membership and integration to NCI Comprehensive Cancer Centers

Several with informal or individual interactions

Other cooperative veterinary clinical trial groups (private practice and academic-led)

Spontaneous cancer in dogs: why is it relevant?

Approximately 78 million dogs in US households

- **Over 1 million will develop cancer each year**

Many cancers are similar to those that occur in people:

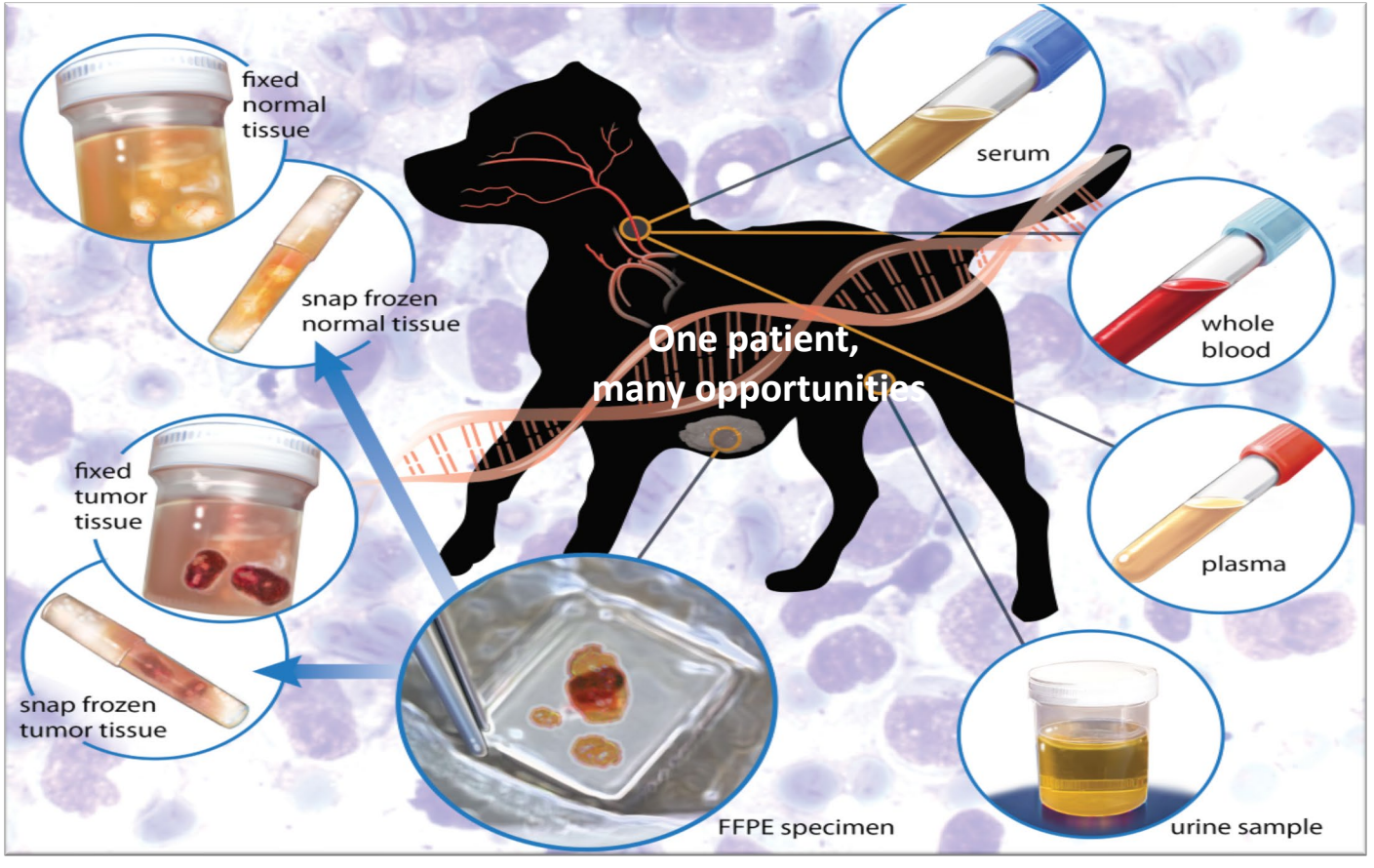
- **Non-Hodgkin's lymphoma, melanoma, osteosarcoma, soft tissue sarcoma, muscle-invasive bladder cancer, brain tumors**

Owners are increasingly interested in more advanced therapeutics and access to clinical trials for their pets

- **Surgery, chemotherapy, radiation therapy, small molecule RTK inhibitors, canine-specific immunotherapies**

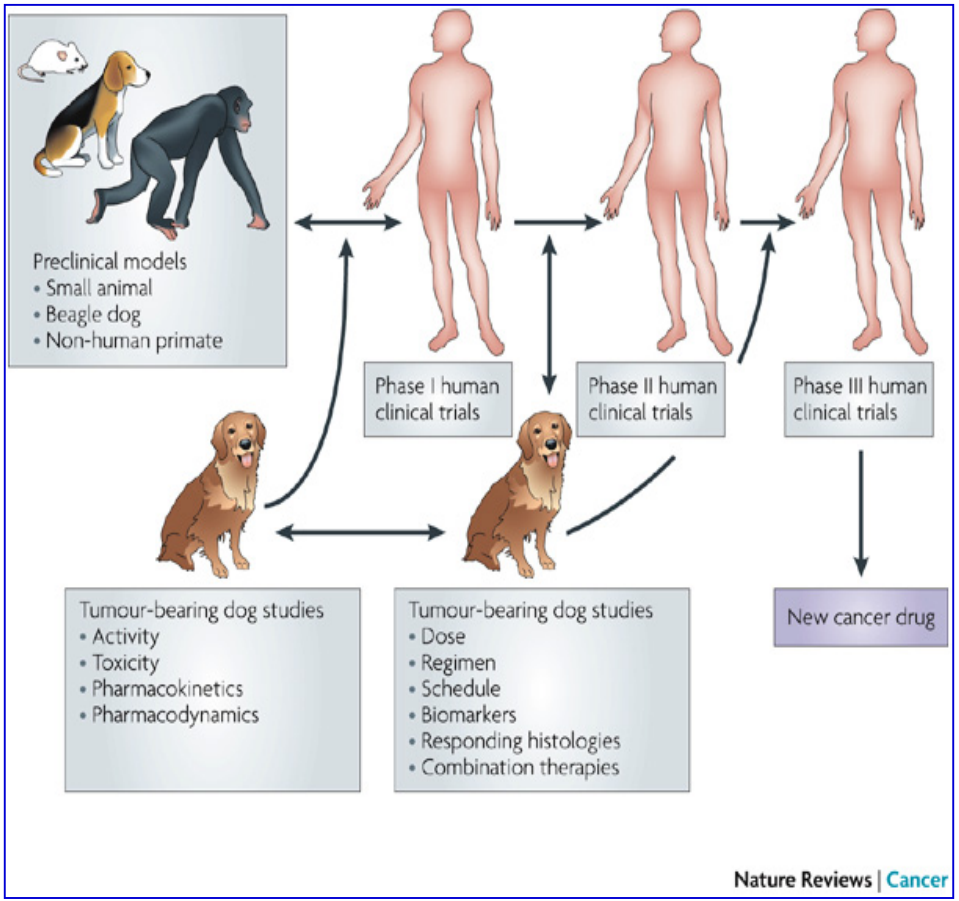
Why consider a comparative oncology approach to cancer drug development?

Comparable genetic etiopathogenesis	Greater synteny between dog/human vs. rodent/human Similar gene expression alterations in cancer
Comparable signal transduction pathways	Similar druggable targets identified Similar angiogenic and apoptotic pathways
Spontaneous tumors, outbred population	Recapitulates heterogeneity in human tumors Recurrence, metastasis, resistance to therapy common
Lower relative cost	GMP quality material not always necessary Pre-IND work highly valuable, particularly for early efficacy signals
Population less heavily pretreated	Higher patient performance status, more accurate AE assessment and less acquired resistance
Body size of companion species	Similar imaging and treatment modalities used Opportunity for repeated tissue and fluid sampling



- Large-volume biologic samples collected routinely via validated SOPs during comparative oncology clinical trials
- Access to canine-specific assays and reagents through the COTC Pharmacodynamic (PD) Core laboratory (Colorado State University)

A Comparative and Integrated Approach to Cancer Drug Development



COTC001: Evaluation of RGD targeted delivery of phage expressing TNF-α in tumor bearing dogs

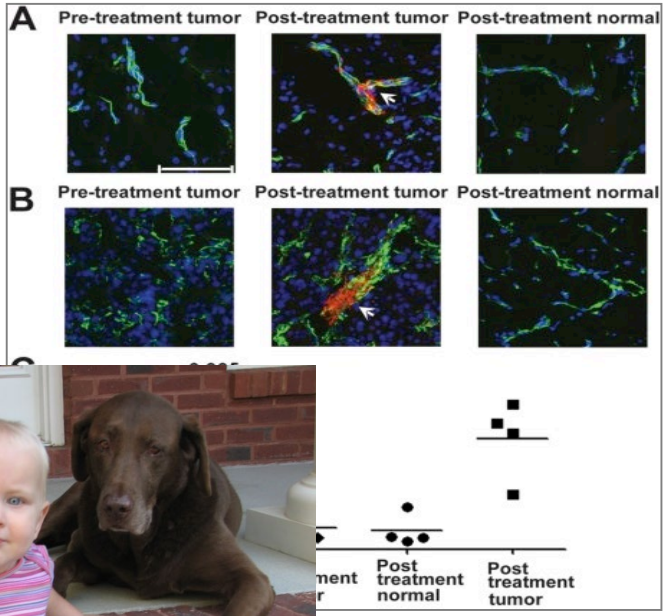
Phase I study of TNFα adeno-expression cassette with RGD motif targeting αvβ3 integrin receptors on tumor neo-vessels.

Co-localization of RGD-TNF particles was present within tumor vascular endothelium, but not in the tumor cells or blood vessels in normal tissues.

hTNFα levels increased in p treatment tumor biopsies compared to pre-treatmer tumor biopsies.

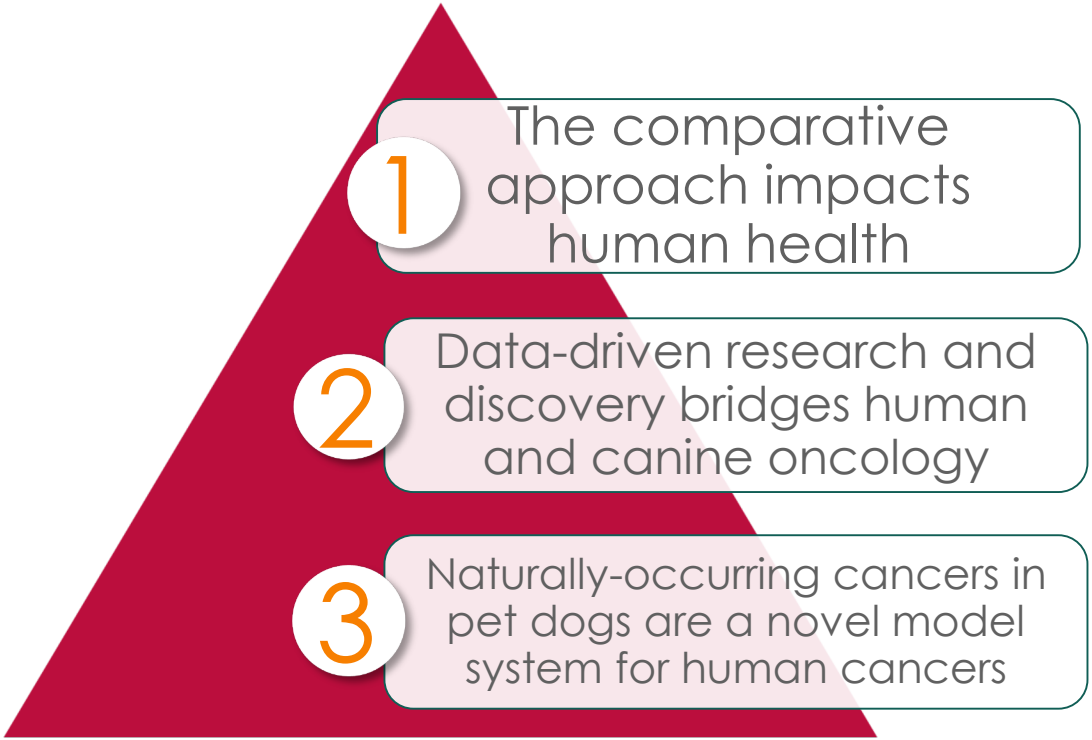
<u>Informed</u> phase I trials in p

Green: anti-CD31 Red: anti-phage



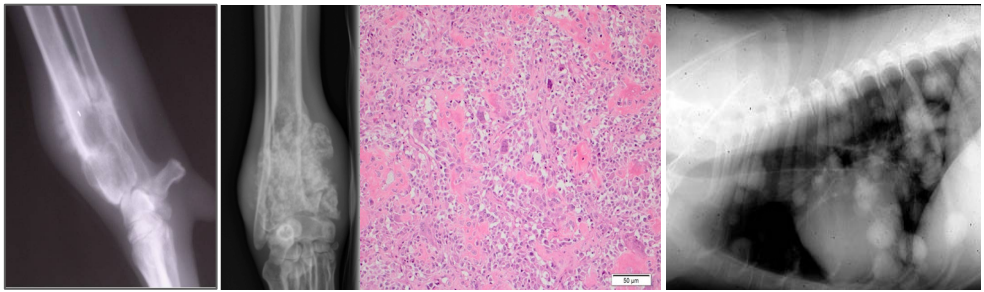
Paoloni et al, PLOS One, 2009

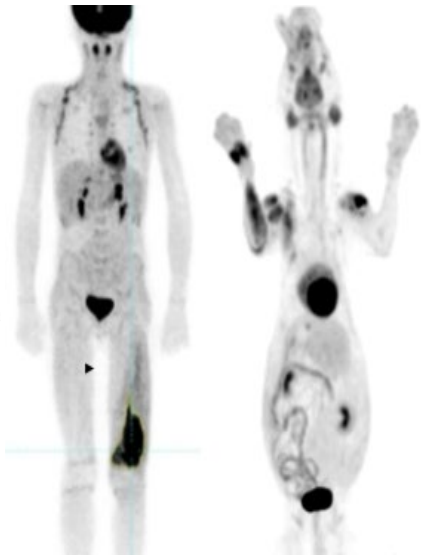
Comparative oncology's challenge: to move past observations and into action



Canine Osteosarcoma

- >10,000 middle-old age, large and giant breed dogs in the US/year vs. ~ 1000 pediatric/AYA cases
- Median Survival Time: 10-14 months - majority develop **metastatic disease**
- Shares many clinical and molecular features with pediatric osteosarcoma
- Canine model recognized as a key component of discovery process for new therapies for children

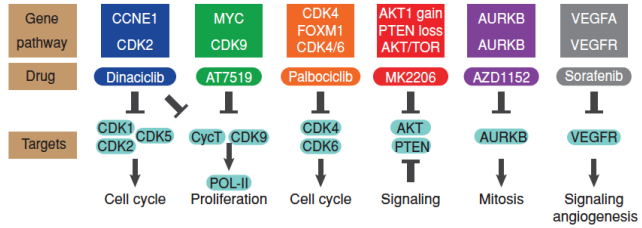




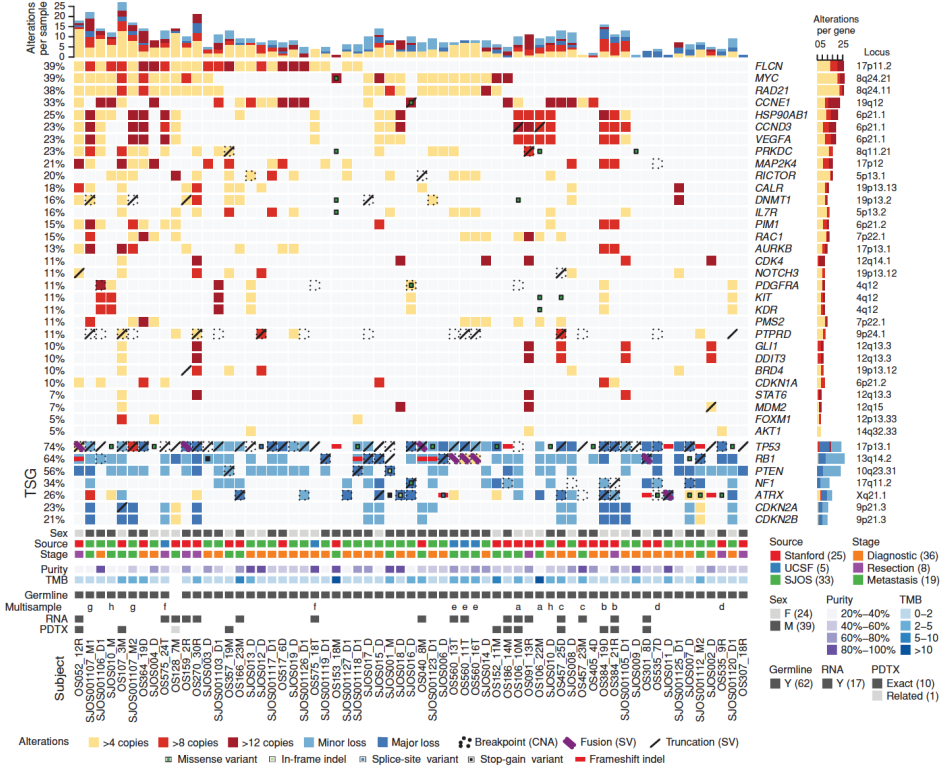
Images courtesy of Nicola Mason/UPenn and Kristen Weishaar/CSU

Genome-Informed Targeted Therapy for Osteosarcoma

Leanne C. Sayles[1], Marcus R. Breese[1], Amanda L. Koehne[1], Stanley G. Leung[1], Alex G. Lee[1], Heng-Yi Liu[1], Aviv Spillinger[1], Avanthi T. Shah[1], Bogdan Tanasa[1], Krystal Straessler[1], Florette K. Hazard[2], Sheri L. Spunt[3], Neyssa Marina[3], Grace E. Kim[4], Soo-Jin Cho[4], Raffi S. Avedian[5], David G. Mohler[5], Mi-Ok Kim[6,7], Steven G. DuBois[8], Douglas S. Hawkins[9], and E. Alejandro Sweet-Cordero[1]



- In-depth genomic profiling of human OS allows generation and selection of appropriate PDX models, and rational testing of therapeutic strategy
- Companion strategy in dogs can identify translationally-relevant canine OS subtypes for targeted recruitment into clinical trials

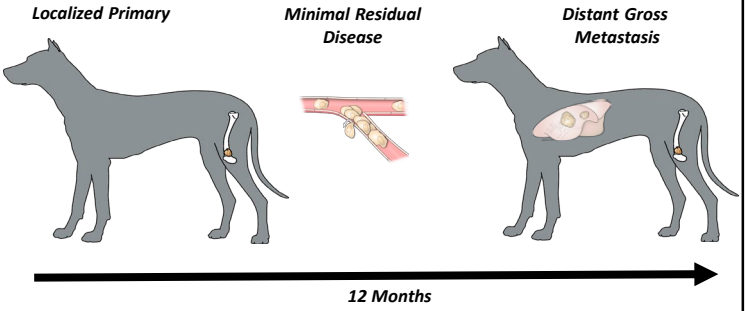


A Comparative Approach to Osteosarcoma Drug Development: Translational studies of agents designed to improve outcomes for dogs and humans

Canine OS Trials

Minimal residual disease studies

- *Comparative Oncology Trials Consortium*
- *Prioritize agents for human MRD/adjuvant based studies of metastatic progression*



Enrolled ~450 canine patients on 3 trials over ~3.5 years

Therapeutic approaches include:
Novel biologics/vaccines
Rapalog inhibition of mTOR
Metabolic targeting of metastatic cells

Early Phase Trials

Measurable Disease

Later Phase Trials

Minimal Residual Disease

DOG^2 project goals:

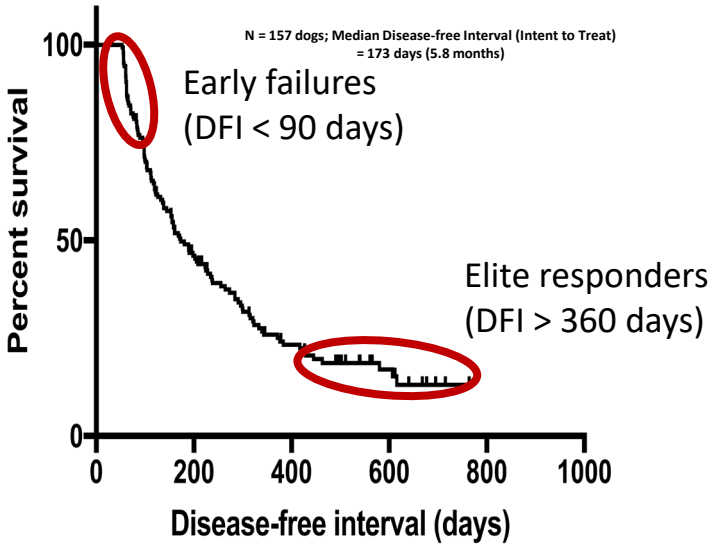
- Build out a comprehensive comparative dataset describing the molecular landscape of canine OS
  - Define molecular subtypes
  - New druggable targets

- Leverage existing canine OS biospecimen repository
  - Tumor:normal; tumor:met; all treatment-naïve and outcome-linked; same method of treatment

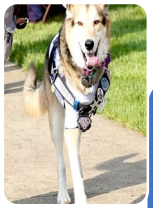
- n = 72
  - 36 each early failures/elite responders
  - RNAseq, WES, low-pass and deep WGS

- n = 25 tumor:met pairs

dog^2 Deciphering the Osteosarcoma Genome in Dogs



The National Cancer Institute Comparative Oncology Trials Consortium



Prioritize therapeutic approaches to study in canine OS clinical trials

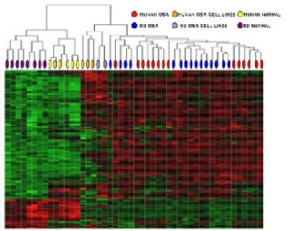
COG input

Define genomic landscape of canine OS with COP biospecimen repository

Integrate with human OS data (NCI TARGET)

TARGET

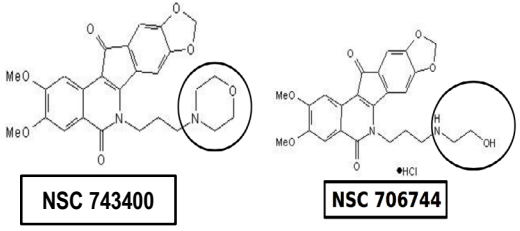
Identify new druggable targets



Interrogate with preclinical (mouse) models

A Comparative Approach: Leveraging existing tools and expertise to identify new approaches for pediatric OS

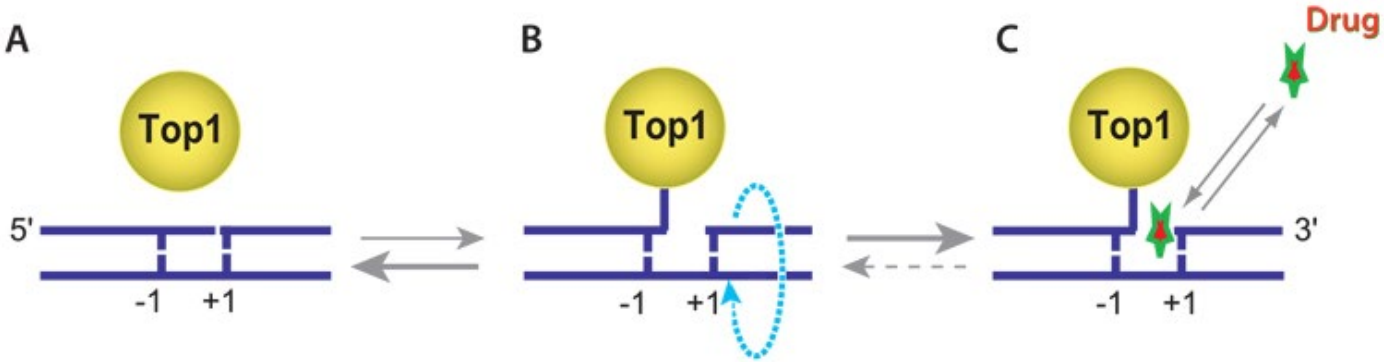
Prioritization of a lead compound



- Study sponsored by DCTD
- 400 & 776 most promising based on preclinical data
- Biomarker: Induction of γH2AX foci formation

1. **Can indenoisoquinolines be safely administered to tumor-bearing dogs?**
2. **What are the comparable toxicity profiles of the three indenoisoquinolines in tumor-bearing animals?**
3. **What are comparative PK profiles and correlative PD marker(s) for response?**
4. **Are indenoisoquinolines active in a naturally occurring canine model of non-Hodgkin's lymphoma?**

Indenoisoquinolines: novel inhibitors of topoisomerase 1 (TOP1)



TOP1 empirically validated as target by success of camptothecin derivatives (topotecan and irinotecan)

Topoisomerase (Top1) relaxes DNA by generating single-stranded breaks in the DNA backbone, forming cleavage complexes

Top1 inhibition ➔ cytotoxicity:

1. Drug binds reversibly to cleavage complex to slow down DNA re-ligation
2. Upon collision with replication fork or transcription machinery, complex becomes irreversibly “trapped” and induces DS DNA breaks

Why develop the indenoisoquinoline class?

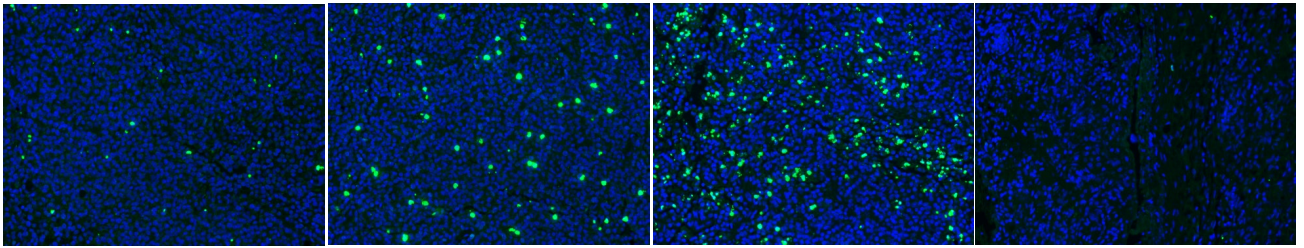
Camptothecins (CPTs)

- Inactivated at physiologic pH by lactone hydrolysis
- Long infusion times needed to overcome reversibility of binding
- Drug efflux ABCG2 substrates
- Murine bone marrow progenitors resistant to CPTs

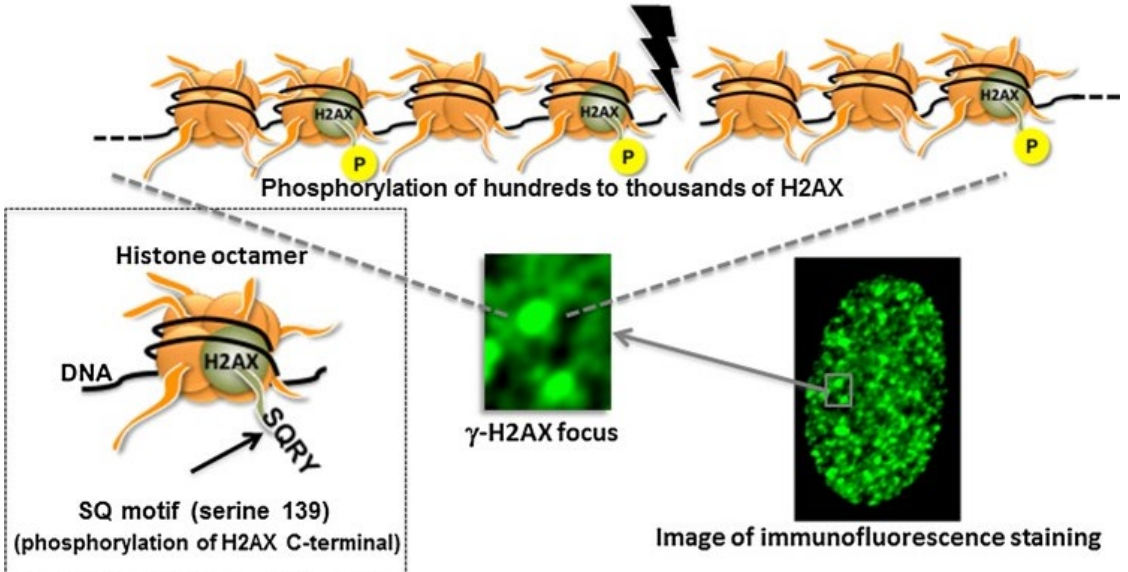
Indenoisoquinolines

- Stable in blood
- Persistent enzyme-DNA cleavage complexes at novel sites compared to CPTs
- Not/lesser substrates of ABCG2
- Animal models (mouse, dog) more predictive of toxicity profile

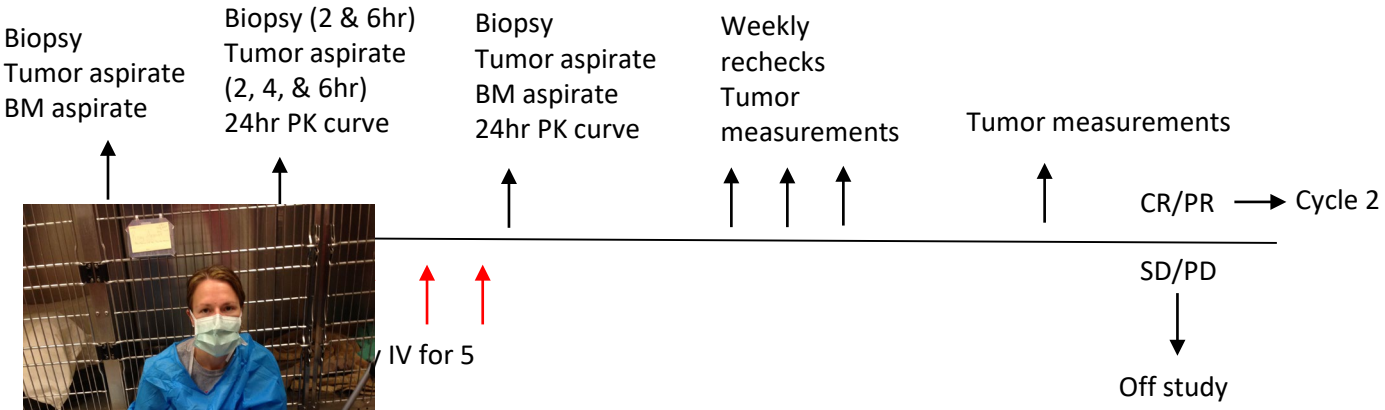
Indenoisoquinolines: γH2AX as pharmacodynamic (PD) readout



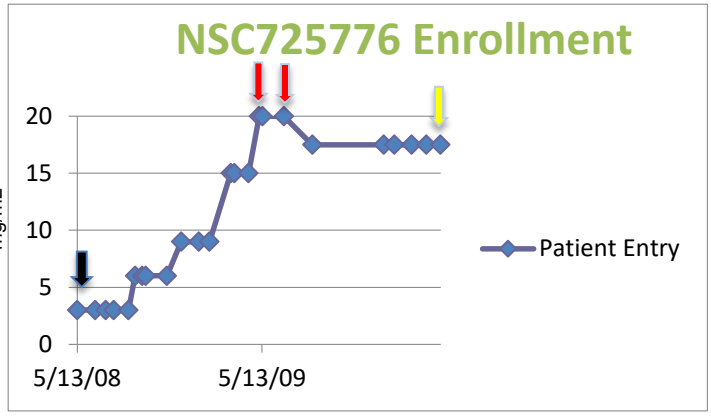
Predose | Day 1, 2Hr | Day 1, 6Hr | Day 6

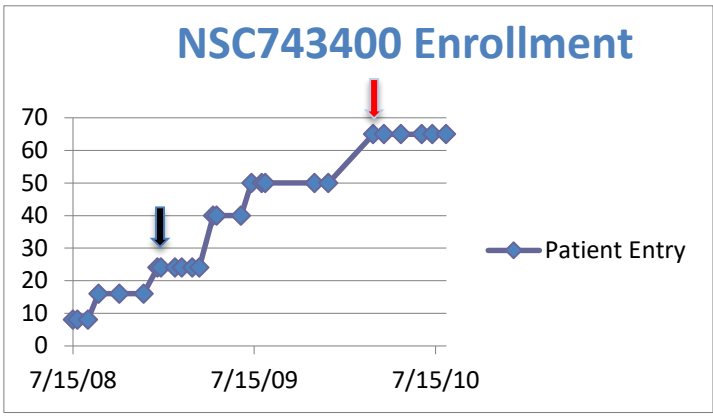


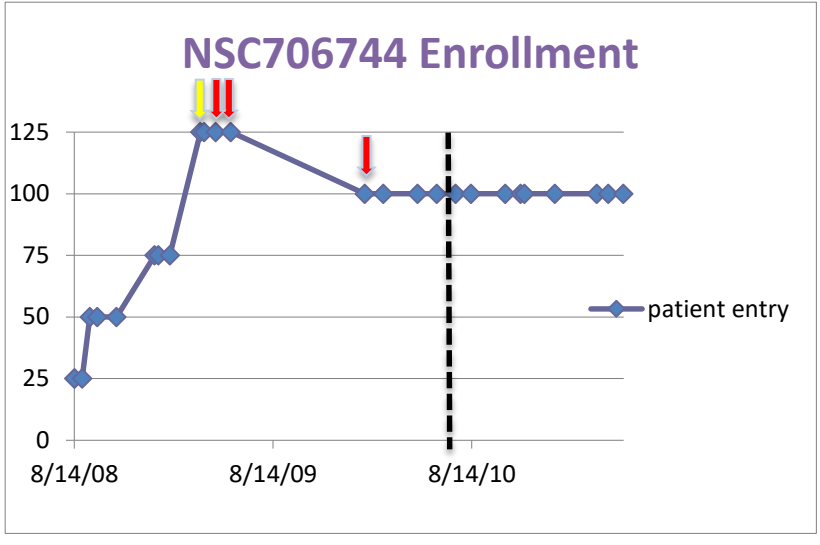
COTC007b: A multicenter trial, open-label prospective preclinical trial of indenoisoquinolines in pet dogs with lymphoma



ort y)	NSC 743400	NSC 706744	NSC 725776
	8	25	3
	16	50	6
	24	75	9
4	40	125	15
5	50	150	20







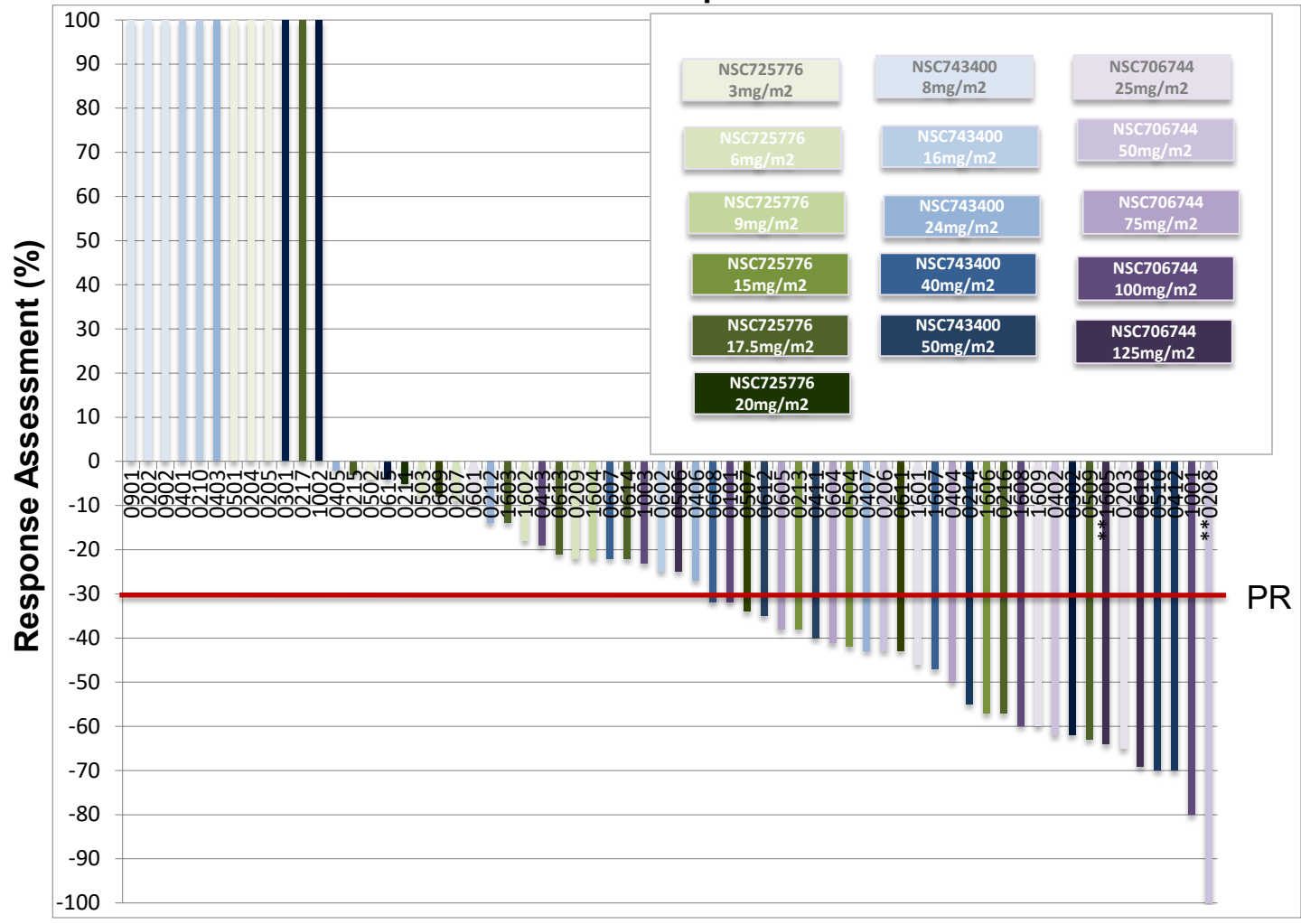
Grade 5 event
Grade 4 event
Grade 3 event

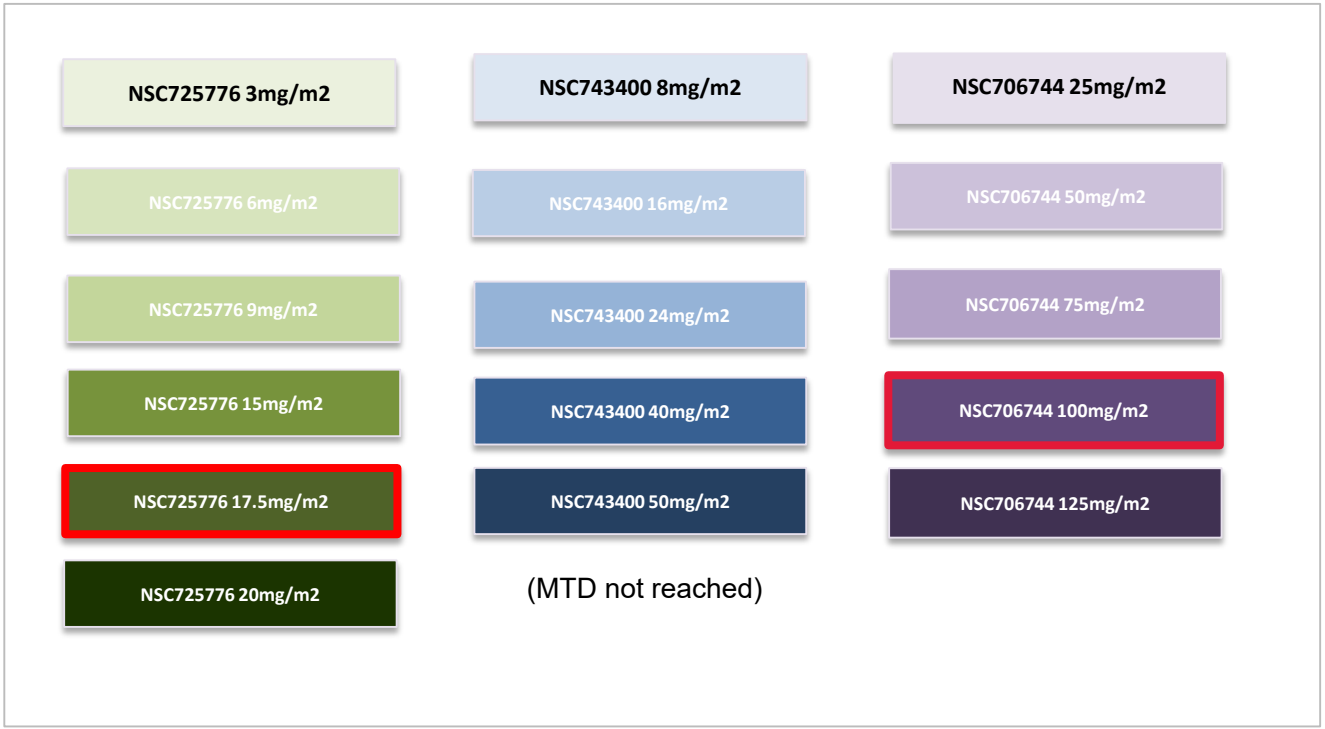
9 COTC sites; 84 dogs enrolled

Dose escalation complete: 69 dogs treated

Cohort expansion complete: 13 dogs treated

Best Overall Response





Overall response rate (PR or better)

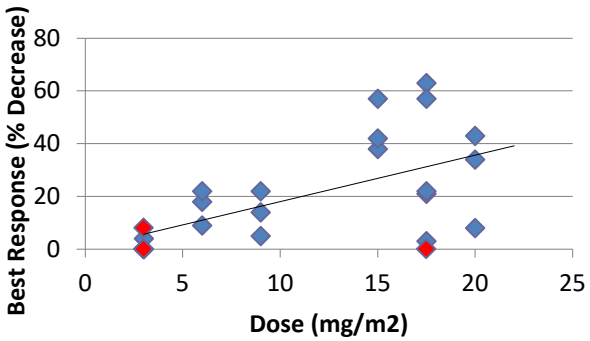
7/23 (30%)	9/23 (39%)	18/23 (78%)

Response at the MTD

2/6 (33%)	N/A	8/11 (73%)

Dose vs. Best Clinical Response

NSC725776



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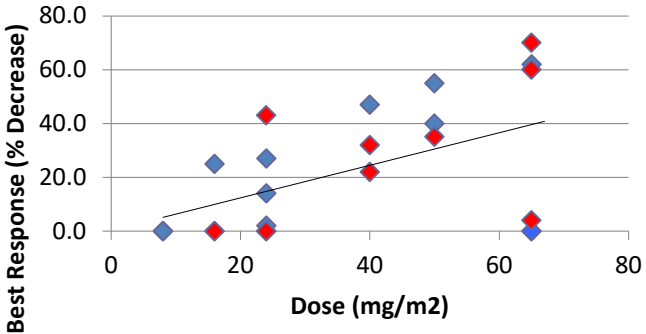

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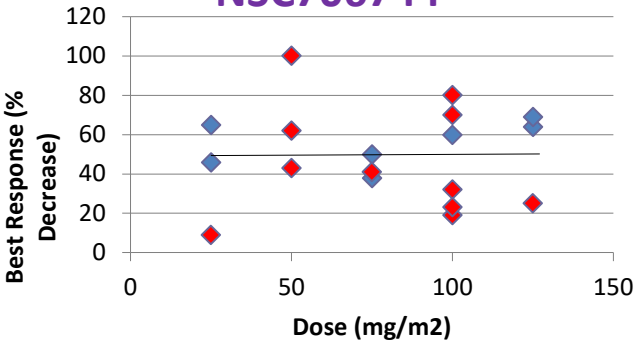
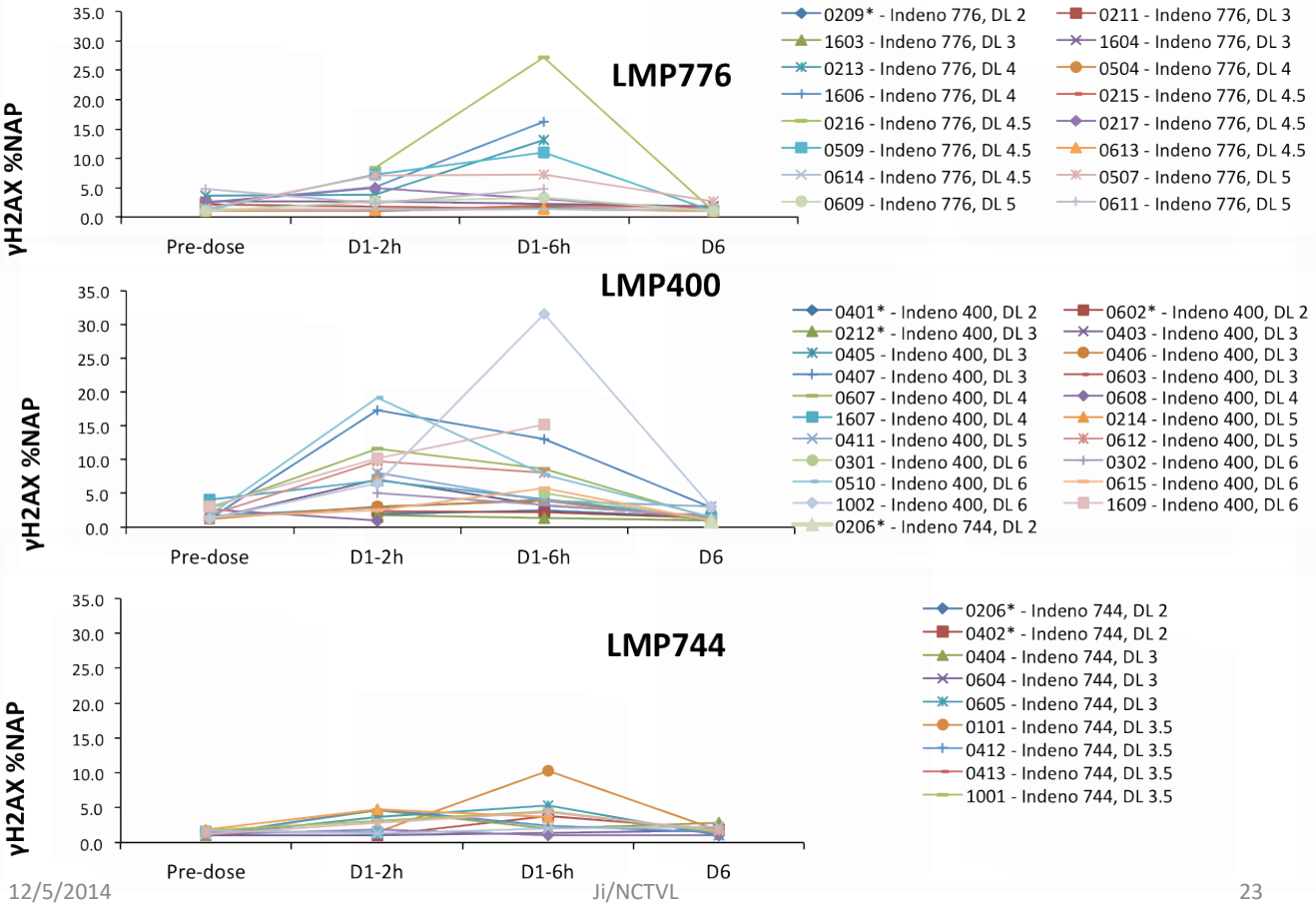


- Evidence of dose response for LMP 776 & 400
- Early-cohort responders with LMP 744 suggest dose-response may be plateaued
- Non-responders (SD + PD) across dose range with LMP 776 & 400

Red=Previously treated, blue=naïve disease

gH2AX at pre-dose, 2 hr, 6 hr, Day 6



Study Summary

1. **Can indenoisoquinolines be safely administered to tumor-bearing animals?**
   - Yes
2. **What are the comparable toxicity profiles of the three indenoisoquinolines in tumor-bearing animals?**
   - Toxicity profiles are similar across all 3 agents
   - No unexpected adverse events
3. **What are comparative PK profiles and correlative PD marker(s) for response?**
   - 744 exhibits 10x higher tumor drug accumulation than 766 and 400
   - γH2AX signal does not correlate for biologic response for 744
   - TOPO-1 inhibition may not be 744's main mechanism of action

4. **Are indenoisoquinolines active in a naturally occurring model of non-Hodgkin's lymphoma?**
   - 744 overall response rate is 2x that of 776 and 400

What lies ahead for comparative oncology's role in cancer research and drug development?

- Emphasis on continuing the scientific dialogue on applicability and validity of the dog model of cancer for strategic advancement of novel agents

- Maintain the highest standards for clinical trial design, execution and reporting

- Continue developing portfolio of canine-specific reagents and correlative assays to support trial efforts and enhance human translation

Acknowledgements

NIH-NCI Center for Cancer Research
-Molecular Imaging Program (Dr. Peter Choyke, Elaine Jagoda, Baris Turkbey, Dagane Daar, Tieu Hoa, Alicia Forest, Phil Eclarinal, Karen Wong)
-Genetics Branch (Dr. Paul Meltzer)
-Pediatric Oncology Branch (Drs. Javed Khan, Kathy Warren, Rosandra Kaplan, Fernanda Arnaldez)
-Radiation Oncology and Biology Branches (Drs. Murali Cherukuri, Kazu Yamamoto)
-NeuroOncology Branch (Dr. Mark Gilbert, Dr. Mioara Larion, Victor Ruiz)

NIH-NCI Comparative Oncology Program
-Christina Mazcko; Dr. Ling Ren; Dr. Shan Huang; Aswini Cherukuri
-Dr. Hongsheng Wang
-Christine Tran Hoang
-Anusha Kambala

NCI Division for Cancer Treatment & Diagnosis (DCTD)
NIH Divisions of Veterinary Resources (DVR) and Radiation Safety (DRS)
NIH Imaging Probe Development Center (IPDC)

Dr. Chand Khanna
COTC member institutions, investigators, and support staff: past, present and future

Thanks for your attention

Questions?

www.cancer.gov

www.cancer.gov/espanol