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TK216 PHASE 1/2 STUDY IN METASTATIC, RELAPSED/REFRACTORY EWING SARCOMA

Joseph A Ludwig, M.D.
MD Anderson Cancer Center

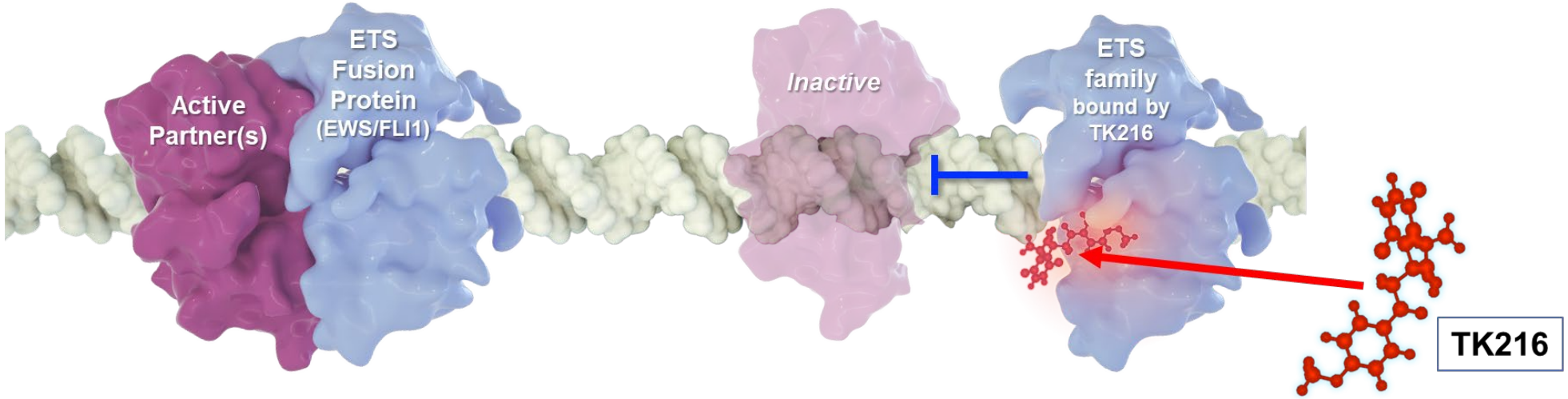
Noah C. Federman[1]; Peter Anderson[2] ; Margaret E. Macy[3] ; Richard F. Riedel[4] ; Lara Davis[5]; Najat C. Daw[6]; Jodi A. Muscal[7]; Aerang Kim[8]; Ravin Ratan[9]; Xen Ianopulos, MD, PhD[10]; James B. Breitmeyer, MD, PhD[10]; Frank J Hsu, MD[10]; and Paul Meyers[11]

[1]Pediatrics, UCLA Medical Center, Los Angeles, CA, USA; [2]Cleveland Clinic Foundation, Cleveland, OH, USA; [3]Pediatrics, Children's Hospital of Colorado, Aurora, CO, USA; [4]Internal Medicine, Duke University Medical Center, Durham, NC, USA; [5]Oregon Health & Science University, Portland, OR, USA; [6]Pediatrics, MD Anderson Cancer Center, Houston, TX, USA; [7]Pediatrics, Texas Children's Hospital, Houston, TX, USA; [8]Children's National Medical Center, Washington, DC, USA; [9]Sarcoma, MD Anderson Cancer Center [10]Oncternal Therapeutics Inc., San Diego, CA, USA.; [11] Memorial Sloan Kettering Cancer Center, New York, NY, USA

DISCLOSURE INFORMATION

- Dr. Ludwig has no conflicts of interest to disclose
- This Ewing sarcoma study is sponsored by Oncternal Therapeutics, Inc., San Diego CA

TK216: A Targeted Inhibitor of ES Fusion Protein



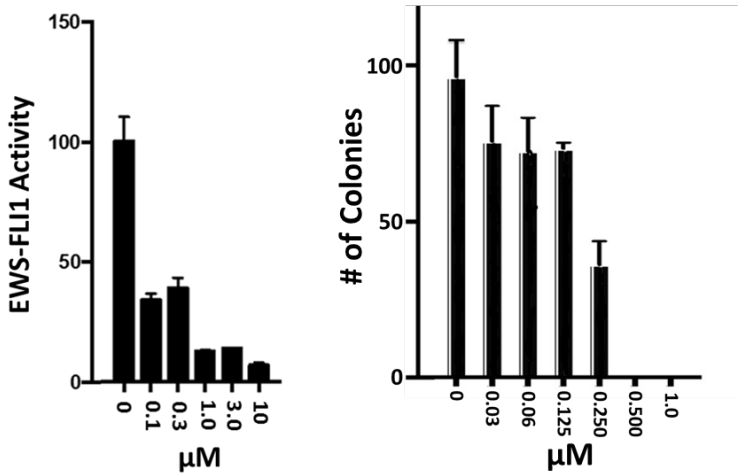
- Major unmet medical need for relapsed or recurrent Ewing sarcoma
- Almost all Ewing sarcomas driven by ETS-family fusion protein (EWS-FLI1, EWS-ERG…)
- TK216 is the first clinical candidate targeting the oncogenic ES fusion protein
- TK216 is believed to disrupt transcriptome formation mediating:
  - Decreased oncogene and increased tumor suppressor transcription
  - Decreased tumor growth and apoptotic cell death

ES = Ewing sarcoma
ETS = E26 Transformation-Specific oncogene family

Erkizan 2009 Nature Medicine
Hong 2013 Oncotarget

Preclinical Activity of ETS inhibitors

TK216 Inhibits Oncogenic Transcription and Cell Proliferation



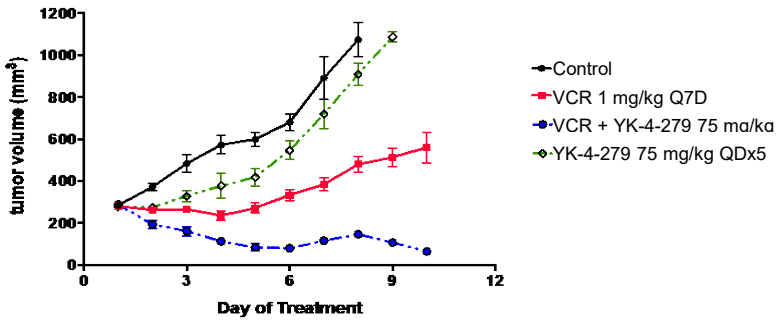
Oncternal data

TK216 Analogue YK-4-279 is Synergistic with Vincristine

In Vitro

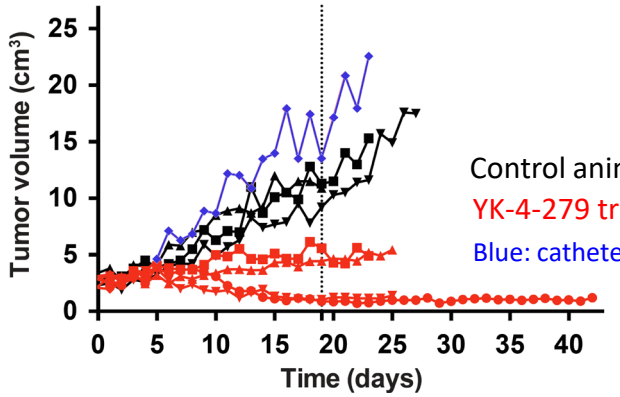
- ↑ G2-M arrest
- ↑ cyclin B1
- ↓ microtubule-associated proteins
- ↑ microtubule depolymerization
- Enhanced apoptosis

In Vivo (A4573 xenograft)

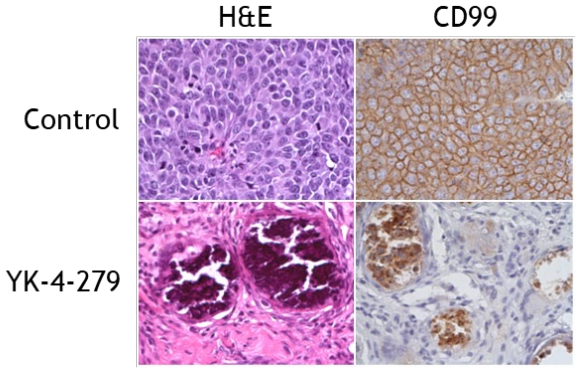


Zollner *et al*, 2017 Science Signaling

TK216 Analogue YK-4-279 Inhibited ES Tumor Growth, Induced Apoptotic Death



Control animals: Black
YK-4-279 treated: Red
Blue: catheter malfunction

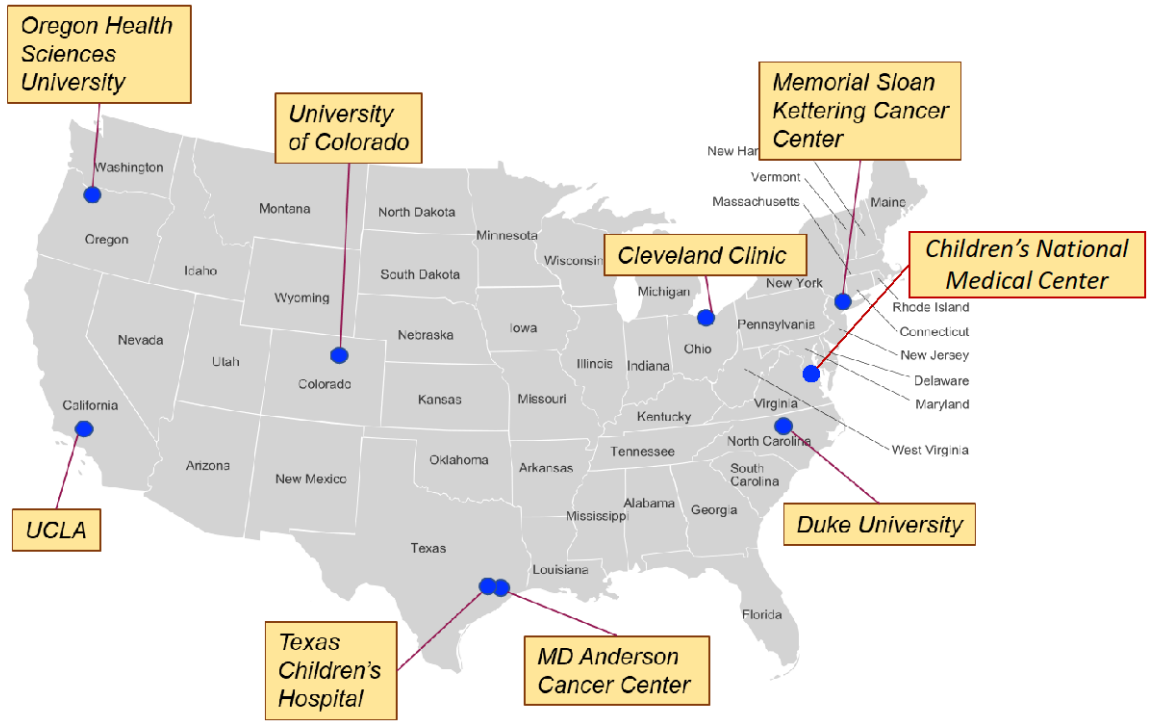


Hong *et al*., 2014 Oncotarget

Preclinical data strongly suggested that prolonged continuous infusion provided optimal antitumor activity

TK216 Phase 1/2 Study Design

- Indication: Recurrent or refractory Ewing sarcoma
- Phase 1/2 clinical trial in 3 Parts:
  - Dose Escalation cohorts:
    - Objectives: PK, DLT, MTD
    - 7 day infusions 18-288 mg/m^2/day
  - Schedule Escalation cohorts:
    - Objectives: PK, Selection of Phase 2 dose
    - 10-14 day infusions 200-220 mg/m^2/day
  - Phase 2 Expansion cohort:
    - Objectives: Tumor responses, PFS
    - RP2D: TK216 200 mg/m^2/day for 14 days
      Vincristine (VCR) 0.75 mg/m^2 day 1



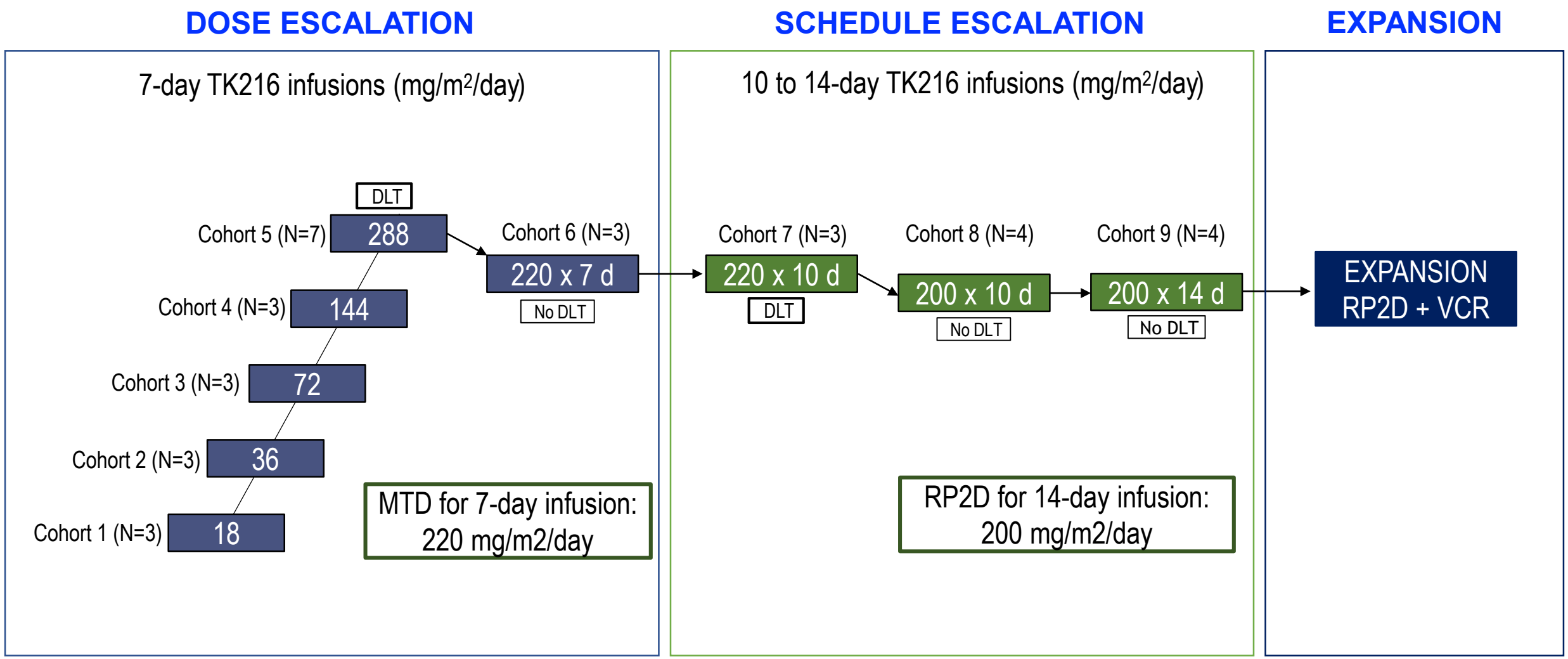
DLT = Dose Limiting Toxicity
MTD = Maximum Tolerated Dose
RP2D = Recommended Phase 2 Dosing regimen

Patient Demographics

N= 56 (Includes patients that have not reached their first evaluation timepoint)		N (%)
Age	Mean (Median) Range	30.9 (29.5) 11 to 77
Gender	Female Male	22 (39.3%) 34 (60.7%)
Race	Asian: Other: White:	7 (12.5%) 5 (8.9%) 44 (78.6%)
Time from Diagnosis to Enrollment (Years)	Median (Range)	3.4 (0.45 to 18)
# Lines of Prior Systemic Therapy*	Median (Range)	3 (1 to 8)
Stage at Enrollment	Stage IV	56 (100%)

*includes all reported systemic therapy patient received for localized and metastatic disease

TK216: Dose and Schedule Escalation Results



Cohort 5: DLT of Neutropenia / Neutropenic fever
Variable and manageable myelosuppression
Early signs of activity with stabilization of disease

Cohort 7: DLT of Neutropenia

Cohort 9: 200mg/m^2/day CIV for 14 days has been well-tolerated.
Vincristine (VCR) allowed starting in cycle 3

Expansion Cohort :
VCR starts in Cycle 1

Frequent (>7%) Adverse Events Considered Related to TK216

Safety population, N=57

Recommended Phase 2 Dose cohorts

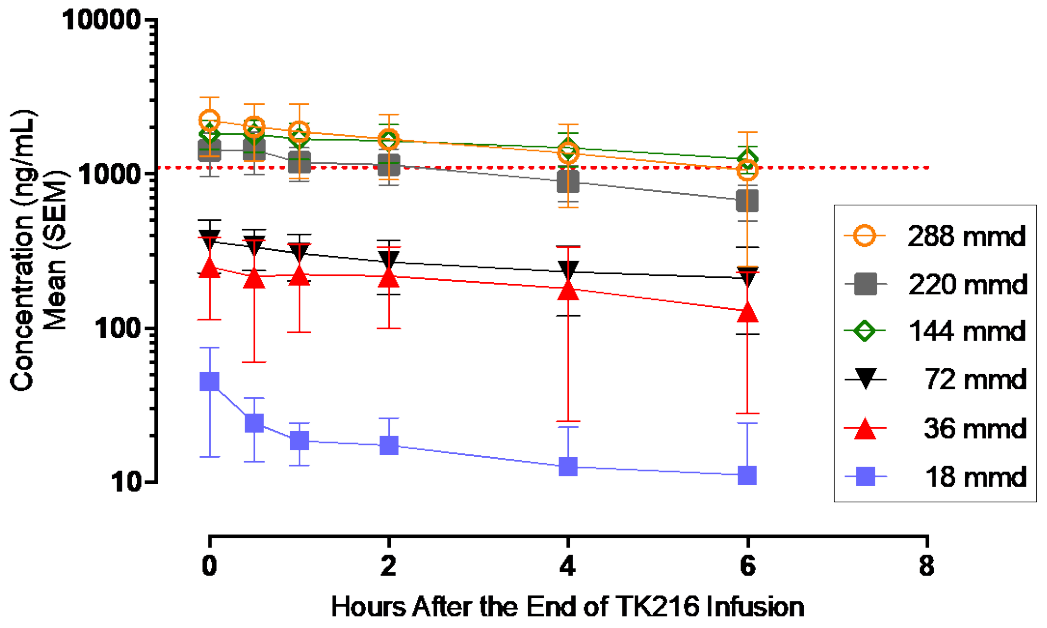
Dose (mg/m^2)	**All Subjects**	18	36	72	144	200	200	220	220	288	Expansion
Duration		7 Days	7 Days	7 Days	7 Days	10 Days	14 Days	7 Days	10 Days	7 Days	14 Days
	N=57	N=3	N=3	N=3	N=3	N=4	N=4	N=3	N=3	N=7	N=24
Number of subjects with an event	**44 (77.2%)**	2 (66.7%)	2 (66.7%)	1 (33.3%)	2 (66.7%)	4 (100%)	4 (100%)	1 (33.3%)	3 (100%)	6 (85.7%)	19 (79.2%)
Preferred Term											
Anaemia	**20 (35.1%)**	0	0	1 (33.3%)	1 (33.3%)	2 (50.0%)	0	0	2 (66.7%)	4 (57.1%)	10 (41.7%)
Fatigue	**16 (28.1%)**	0	0	0	1 (33.3%)	2 (50.0%)	2 (50.0%)	0	3 (100.0%)	2 (28.6%)	6 (25.0%)
Neutrophil count decreased	**16 (28.1%)**	0	0	0	0	3 (75.0%)	1 (25.0%)	0	1 (33.3%)	1 (14.3%)	10 (41.7%)
White blood cell count decreased	**15 (26.3%)**	0	0	0	0	3 (75.0%)	2 (50.0%)	0	1 (33.3%)	2 (28.6%)	7 (29.2%)
Alopecia	**14 (24.6%)**	0	0	0	0	1 (25.0%)	3 (75.0%)	0	1 (33.3%)	2 (28.6%)	7 (29.2%)
Nausea	**11 (19.3%)**	0	1 (33.3%)	0	0	0	1 (25.0%)	0	2 (66.7%)	1 (14.3%)	6 (25.0%)
Neutropenia	**9 (15.8%)**	0	0	0	0	1 (25.0%)	1 (25.0%)	0	2 (66.7%)	3 (42.9%)	2 (8.3%)
Febrile neutropenia	**8 (14.0%)**	0	0	0	0	1 (25.0%)	0	0	2 (66.7%)	3 (42.9%)	2 (8.3%)
Thrombocytopenia	**8 (14.0%)**	0	0	0	1 (33.3%)	0	0	0	2 (66.7%)	3 (42.9%)	2 (8.3%)
Pyrexia	**8 (14.0%)**	0	0	0	1 (33.3%)	1 (25.0%)	0	0	2 (66.7%)	2 (28.6%)	2 (8.3%)
Lymphocyte count decreased	**7 (12.3%)**	0	0	0	0	3 (75.0%)	2 (50.0%)	0	0	1 (14.3%)	1 (4.2%)
Decreased appetite	**7 (12.3%)**	0	0	0	1 (33.3%)	0	0	1 (33.3%)	0	2 (28.6%)	3 (12.5%)
Platelet count decreased	**5 (8.8%)**	0	0	0	0	2 (50.0%)	0	0	1 (33.3%)	0	2 (8.3%)
Leukopenia	**5 (8.8%)**	0	0	0	0	0	0	0	2 (66.7%)	3 (42.9%)	0
Diarrhoea	**5 (8.8%)**	0	0	0	0	0	1 (25.0%)	0	0	2 (28.6%)	2 (8.3%)
Headache	**5 (8.8%)**	0	0	0	0	0	0	0	1 (33.3%)	0	4 (16.7%)
Alanine aminotransferase increased	**4 (7.0%)**	0	1 (33.3%)	0	0	1 (25.0%)	0	0	0	1 (14.3%)	1 (4.2%)
Haematocrit decreased	**4 (7.0%)**	0	0	0	0	2 (50.0%)	1 (25.0%)	0	1 (33.3%)	0	0
Haemoglobin decreased	**4 (7.0%)**	0	0	0	0	2 (50.0%)	1 (25.0%)	0	1 (33.3%)	0	0

Reported treatment-emergent adverse events. Myelosuppression is an expected, on target effect

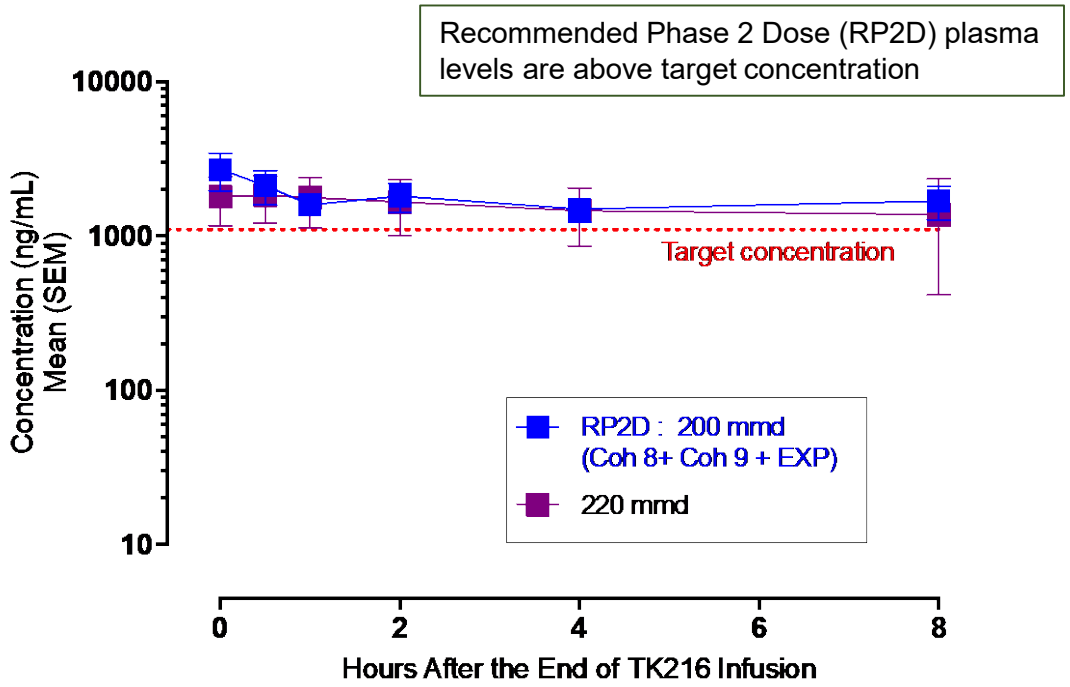
Interim safety analysis, 2 Oct 2020

TK216 Elimination Pharmacokinetics

Dose Escalation (Cohorts 1-6)



Schedule Escalation (Cohorts 7-9) and Expansion



- Time = 0 values reflect steady state at the end of the TK216 infusion
- Half-life is relatively long (8-12 h) with dose proportional increase in concentrations
- Preclinical data suggest that TK216 levels in the 75 to 188 ng/mL range were effective at tumor killing in vitro, and plasma levels in the 265 to ~1500 ng/mL were associated with efficacy in animal tumor model.

Overall Best Clinical Response

Patients were considered evaluable for efficacy if they completed 2 planned cycles of treatment and follow-up tumor assessment studies or had documented or clinical PD following a complete first cycle of therapy.

	Evaluable Patients N= 50	ORR	CR	PR	SD	Disease Control Rate CR+PR+SD
Dose Escalation Cohorts 1-6	21	0	0	0	1	4.8%
Schedule Escalation Cohorts 7-8	6	0	0	0	0	0
RP2D Cohort 9 & Expansion	**23**	**2 (9%)**	**2 (9%)**	**0**	**8 (35%)**	**43%**

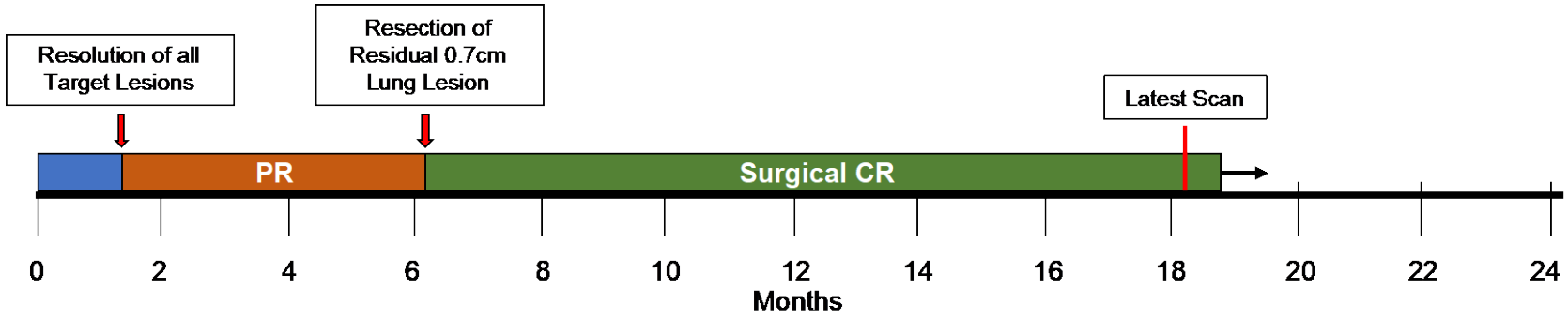
Interim efficacy analysis, 16 Oct 2020

Sustained Complete Response with TK216 in Patient with Extensively Treated Metastatic Relapsed / Refractory Ewing Sarcoma

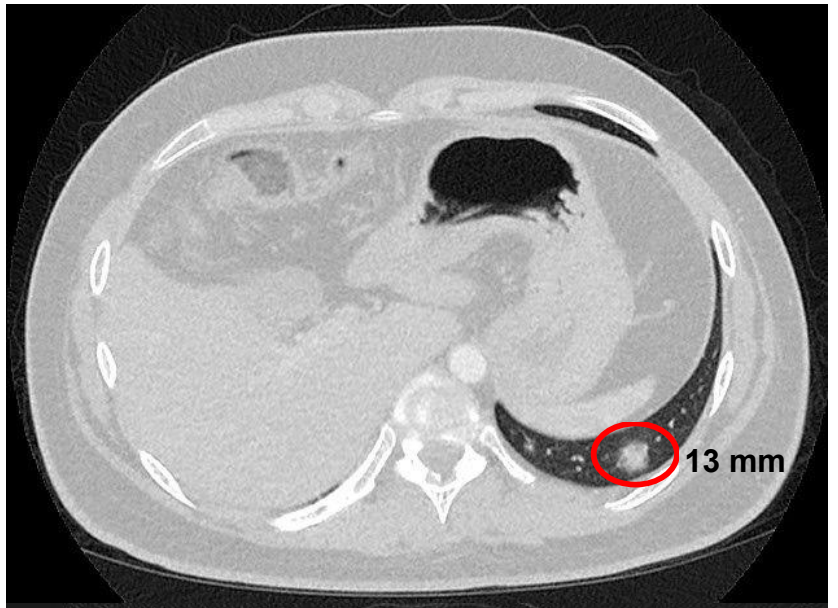
- **Patient:** 19 y.o. male presented with Ewing sarcoma of his clavicle with multiple pulmonary metastases

- **Treatment History:**
  - Tumor genetics: EWSR1-FLI1 fusion
  - Initial Therapy: VDC/IE, surgical resection, RT 50.4 Gy
  - Relapsed 1.5 years after initial diagnosis
  - Multiple recurrences treated with: Whole lung RT, irinotecan/temozolomide, bevacizumab, pazopanib
  - Multiple growing lung nodules at study entry

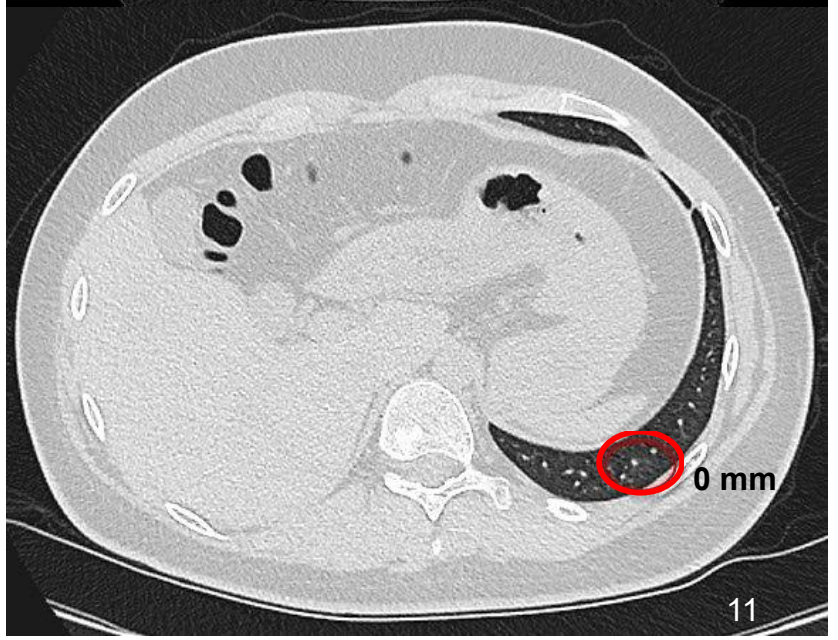
- **TK216 Treatment:** TK216 200 mg/m^2/day CIV for 14-28 days
  - Remains on treatment >1.5 y since enrollment with no evidence of disease (surgical CR)



Baseline

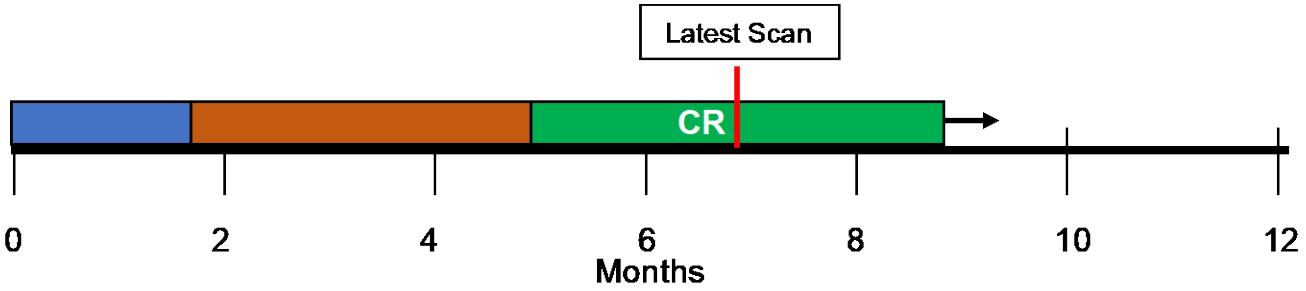


After 2 cycles

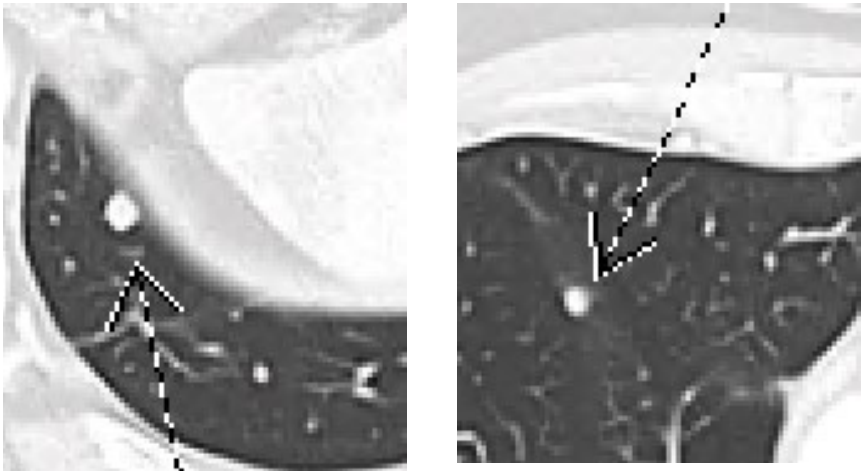


Second Complete Response with TK216
Patient with Heavily Treated Metastatic R/R Ewing Sarcoma

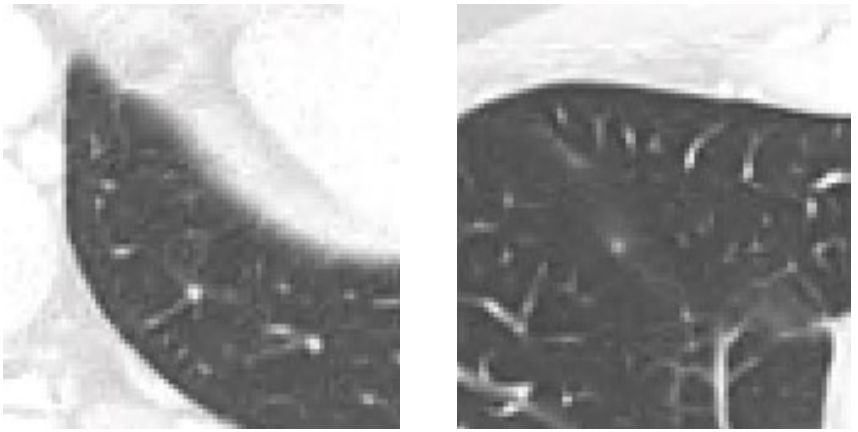
- **Patient:** 51-year-old with Ewing sarcoma
  - Chest CT: 10-cm tumor near the right kidney and multiple lung metastases
  - Tumor Genetics: EWSR1 translocation
- **Extensive Initial Treatment:**
  - Chemo: Vincristine/doxorubicin and ifosfamide (VAI) x10, high-dose ifosfamide x1
  - Surgery: Right nephrectomy and vascular reconstruction
- **Recurrence:** Multiple (>10) new & enlarging lung lesions
  - RECIST 1.1: 20mm
  - Relapsed 1.6 years after initial diagnosis
- **TK216 Treatment:**
  - TK216 200 mg/m^2/day for 14 days + vincristine 0.75 mg/m^2 day 1
  - Treatment ongoing
- **Tumor Response:** Complete Response (CR)
  - After 2 cycles, 90% reduction of all lesions
  - After 6 cycles, CR with resolution of all lesions → ongoing



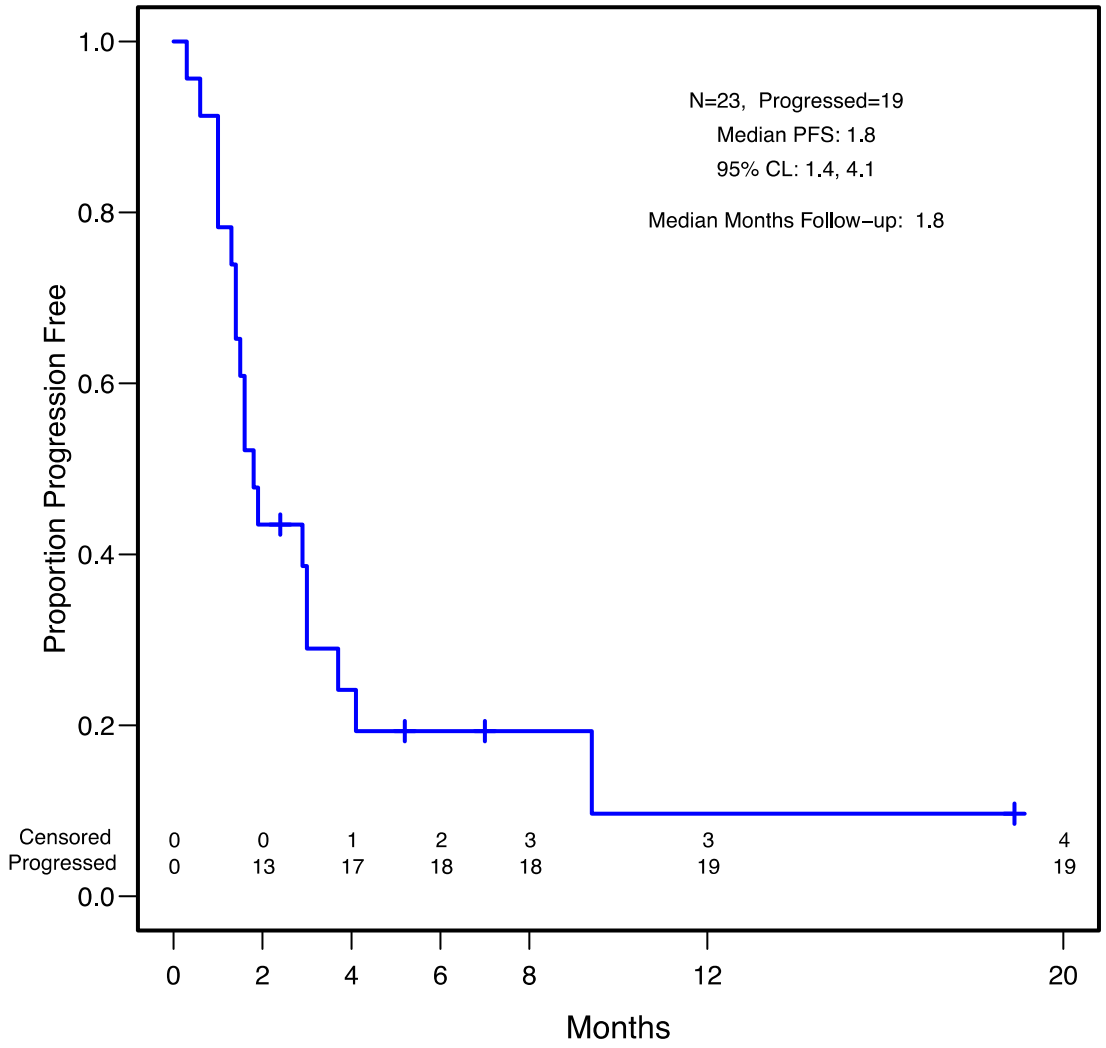
Pretreatment



After 2 cycles



PFS of Evaluable Patients Treated at RP2D in Cohort 9 & Expansion



In a recently reported phase II, double-blind, placebo-controlled trial in previously treated Ewing sarcoma patients, the median PFS of the placebo control group (n= 13) was 3.9 weeks (CI 95%= 3.3-7.3). (REGOBONE, French Sarcoma Group and UNICANCER, ESMO 2020)

Summary

- ***First in human study of TK216:*** A novel agent directed against the ETS family of oncoproteins, whose members are highly expressed in Ewing sarcoma as well as other malignancies

- ***Safety:*** Well-tolerated and manageable safety profile consisting of transient marrow suppression at the current TK216 schedule of 200 mg/m^2/day for up to 14 days +/- VCR

- ***Efficacy***: Phase 2 dose demonstrated early evidence of activity.
  - 2 Complete responses and 8 SD
  - Disease control rate (CR+PR+SD) = 43% (10/23 evaluable patients)
  - The CRs have been durable.

- ***Study Status:*** These objective responses indicate clinical activity of TK216 in R/R, poor risk, heavily pretreated patients with Ewing sarcoma and warrant further investigation. Enrollment of the Expansion Cohort has been expanded and work on potentially predictive biomarkers is underway.