2021 ASCO® ANNUAL MEETING

TK216 FOR RELAPSED/REFRACTORY EWING SARCOMA-INTERIM PHASE 1/2 RESULTS

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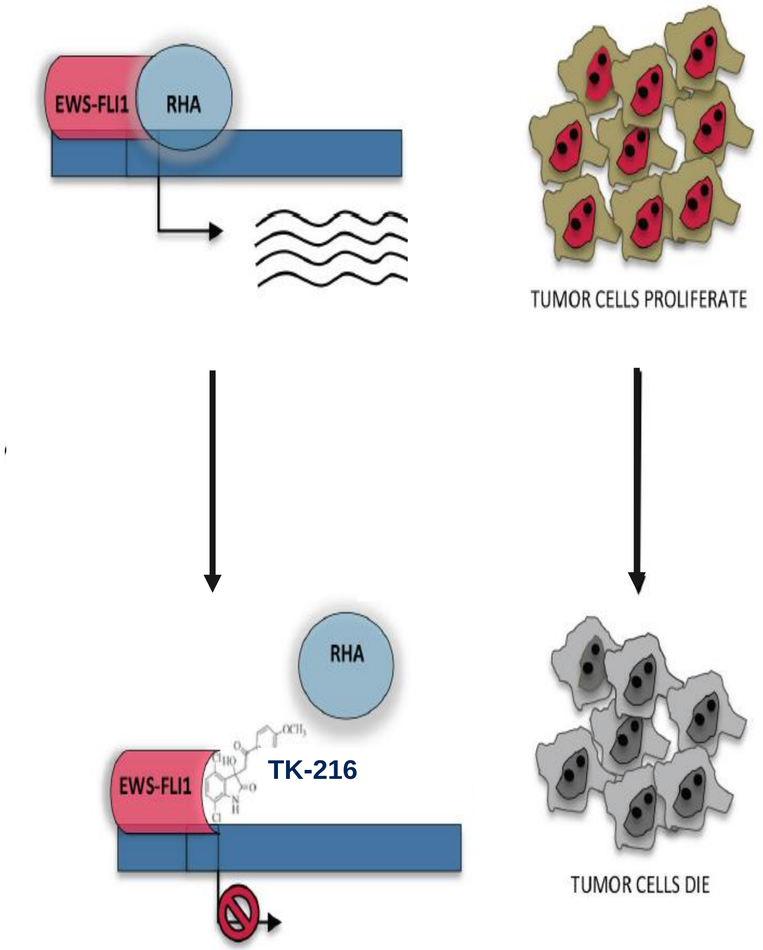
Background

Ewing sarcoma is a rare cancer affecting both children and adults with limited treatment options in the relapsed/refractory setting

- Fusions of the EWS gene and one of five different ETS transcription factors (i.e., EWS-FLI1) are dominant drivers of Ewing sarcoma
- Binding of EWS-FLI1 to RNA helicase A (RHA) is critical for its oncogenic function
- TK216 binds ETS proteins, disrupts protein-protein interactions, inhibits transcriptor factor function, leading to Ewing sarcoma cell death

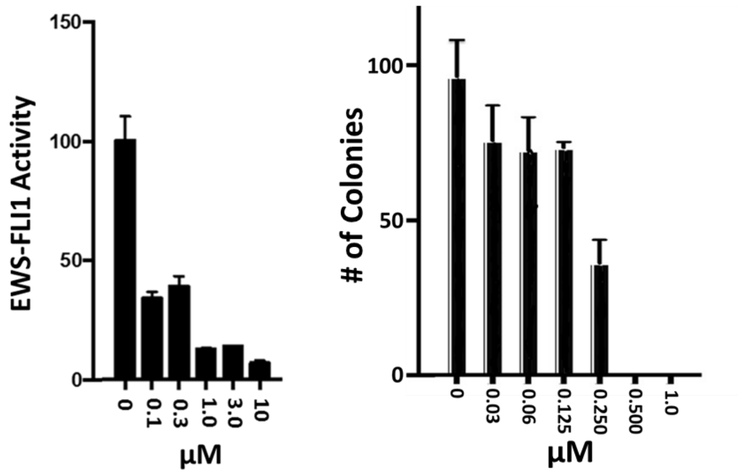


ETS = E26 Transformation-Specific oncogene family

Adapted from Fidaleo et al. Oncotarget, 2016

Preclinical Activity of ETS inhibitors

TK216 Inhibits Oncogenic Transcription and Cell Proliferation



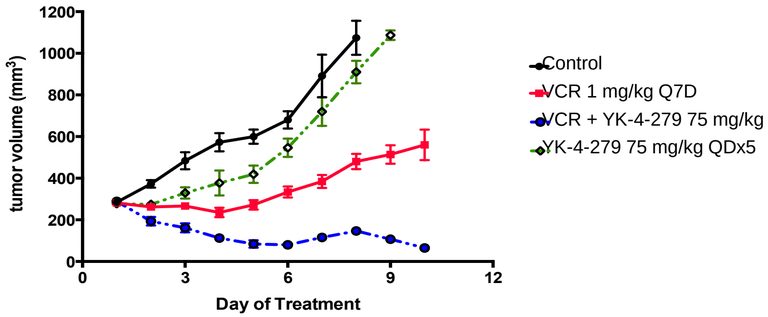
Oncternal data

TK216 Analogue YK-4-279 is Synergistic with Vincristine

In Vitro

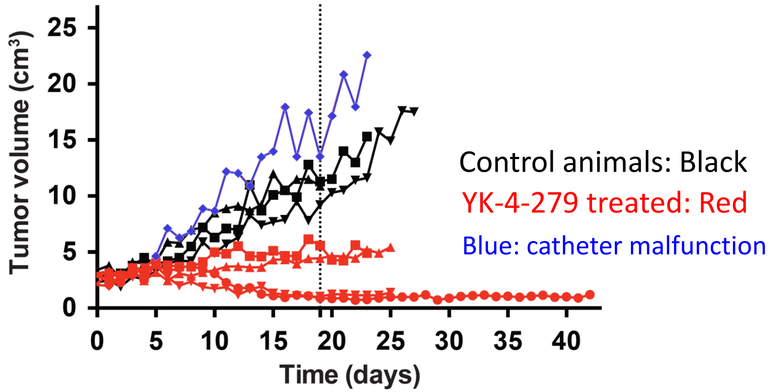
- ↑ G2-M arrest
- ↑ cyclin B1
- ↓ microtubule-associated proteins
- ↑ microtubule depolymerization
- Enhanced apoptosis

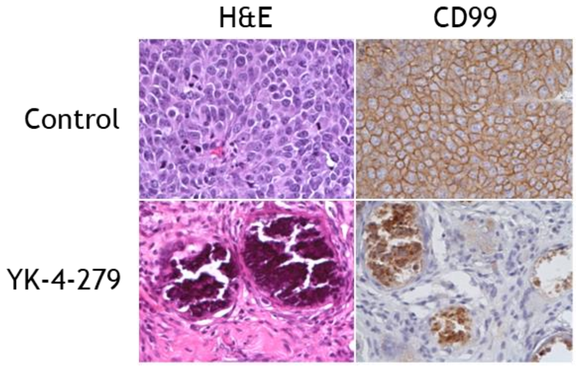
In Vivo (A4573 xenograft)



Zollner *et al*, 2017 Science Signaling

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





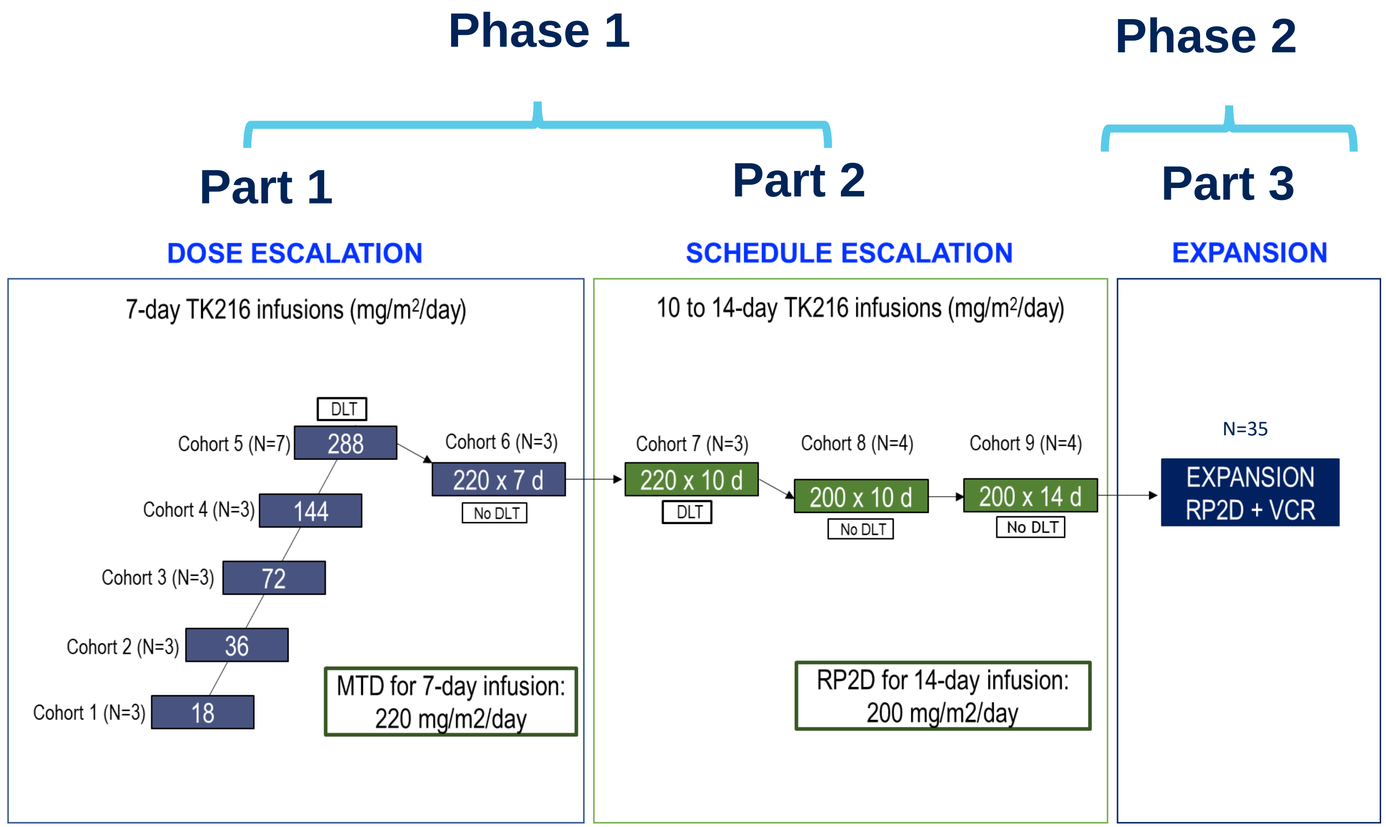
Hong *et al*., 2014 Oncotarget

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

Phase 1/2 Study Design

Population: R/R Ewing sarcoma patients, who have failed standard therapy (no limit to number of prior lines) and have measurable disease at study entry

- Conventional 3+3 design conducted in 3 Parts
- DLTs were neutropenia
- Phase 1 is complete
- RP2D: 200 mg/m²/day continuous IV infusion x 14 days
- Vincristine 0.75 – 1.5 mg/m² on cycle 1 day 1
- Phase 2 Expansion (Part 3) enrolling



R/R= relapsed or refractory; DLT= dose limiting toxicity; RP2D= recommended Phase 2 dose

Demography and Baseline Characteristics

	All Patients n=68	Cohort 9 & Expansion (RP2D) n=39
Median Age (years)	27.0 (11.0, 77.0)	27.0 (11.0, 77.0)
Male, n (%)	43 (63.2)	25 (64.1)
ECOG* 0-1, n (%)	52 (96.3)	29 (93.5)
Median time from diagnosis to study start (years)	3.4 (0.4, 18.0)	3.4 (0.4, 18.0)
Prior surgery, n (%)	53 (77.9)	32 (82.1)
Prior radiotherapy, n (%)	57 (83.8)	34 (87.2)
Median number of prior systemic treatments	3.0 (1.0, 9.0)	3.0 (1.0, 8.0)
Metastases at study entry, n (%)	67 (98.5)	39 (100)
• Bone only	6 (8.8)	2 (5.1)
• Lung only	31 (45.6)	21 (53.8)
• Bone and Lung only	10 (14.7)	8 (20.5)
• Other location	20 (29.4)	8 (20.5)

Data Cut: 16APR2021; *ECOG (Eastern Cooperative Oncology Group) performance score was evaluated in 54 and 31 all treated and Cohort 9 & Expansion patients, percentage is based on number of patients with ECOG evaluated; Median estimates are shown with (min, max)

Population: Heavily pre-treated and high disease burden

Safety: Treatment Emergent AEs ≥ 20% (regardless of causality)

	All patients n=68			Cohort 9 & Expansion (RP2D) n=39		
	All Grades n (%)	Grades 1-2 n (%)	Grades ≥3 n (%)	All Grades n (%)	Grades 1-2 n (%)	Grades ≥3 n (%)
Number of patients with an event	66 (97.1)	22 (32.4)	44 (64.7)	37 (94.9)	11 (28.2)	26 (66.7)
Anemia	34 (50.0)	14 (20.6)	20 (29.4)	18 (46.2)	6 (15.4)	12 (30.8)
Neutropenia	32 (47.1)	8 (11.8)	24 (35.3)	21 (53.8)	7 (17.9)	14 (35.9)
Fatigue	28 (41.2)	25 (36.8)	3 (4.4)	16 (41.0)	15 (38.5)	1 (2.6)
Leukopenia	26 (38.2)	5 (7.4)	21 (30.9)	16 (41.0)	3 (7.7)	13 (33.3)
Pyrexia	24 (35.3)	24 (35.3)	0	11 (28.2)	11 (28.2)	0
Alopecia	21 (30.9)	21 (30.9)	0	16 (41.0)	16 (41.0)	0
Nausea	21 (30.9)	21 (30.9)	0	14 (35.9)	14 (35.9)	0
Headache	17 (25.0)	16 (23.5)	1 (1.5)	12 (30.8)	12 (30.8)	0
Thrombocytopenia	15 (22.1)	7 (10.3)	8 (11.8)	5 (12.8)	3 (7.7)	2 (5.1)
Constipation	14 (20.6)	13 (19.1)	1 (1.5)	9 (23.1)	8 (20.5)	1 (2.6)

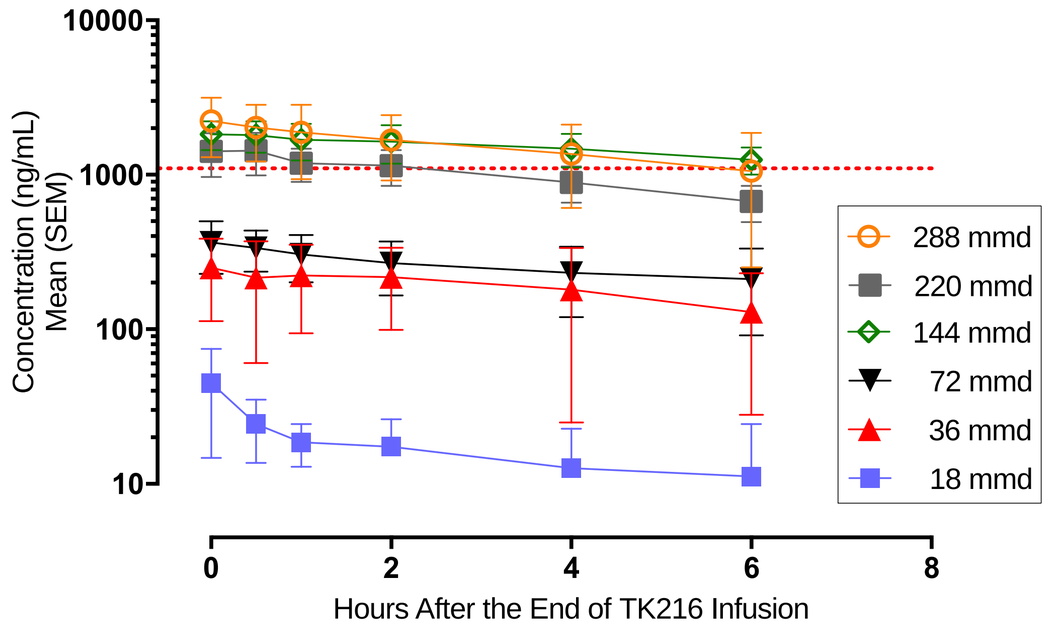
Data Cut: 16APR2021; 0% (0/68) Grade ≥3 TEAEs led to drug discontinuation; Dose not changed was the action taken for TEAEs in 92.6% (63/68); SAEs occurred in 36.8% (26/68), of which 0% (0/68) led to drug discontinuation

TK216 +/- vincristine has a tolerable safety profile

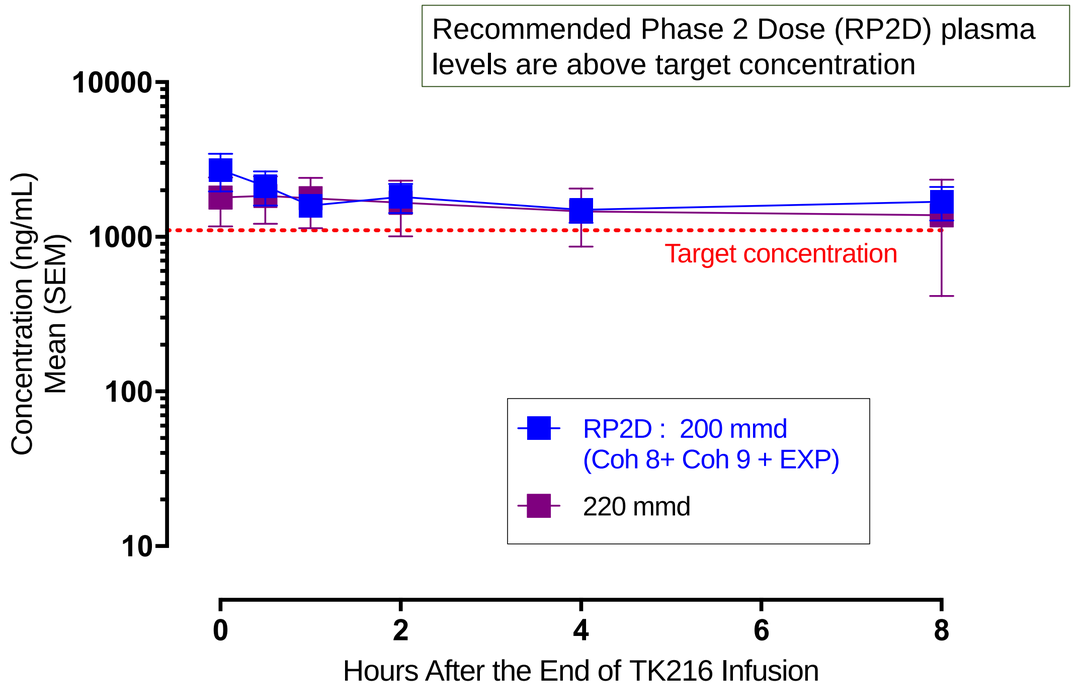
Myelosuppression is the primary safety observation which is transient, reversible, and responsive to growth factors

TK216 Elimination Pharmacokinetics

Dose Escalation (Cohorts 1-6)



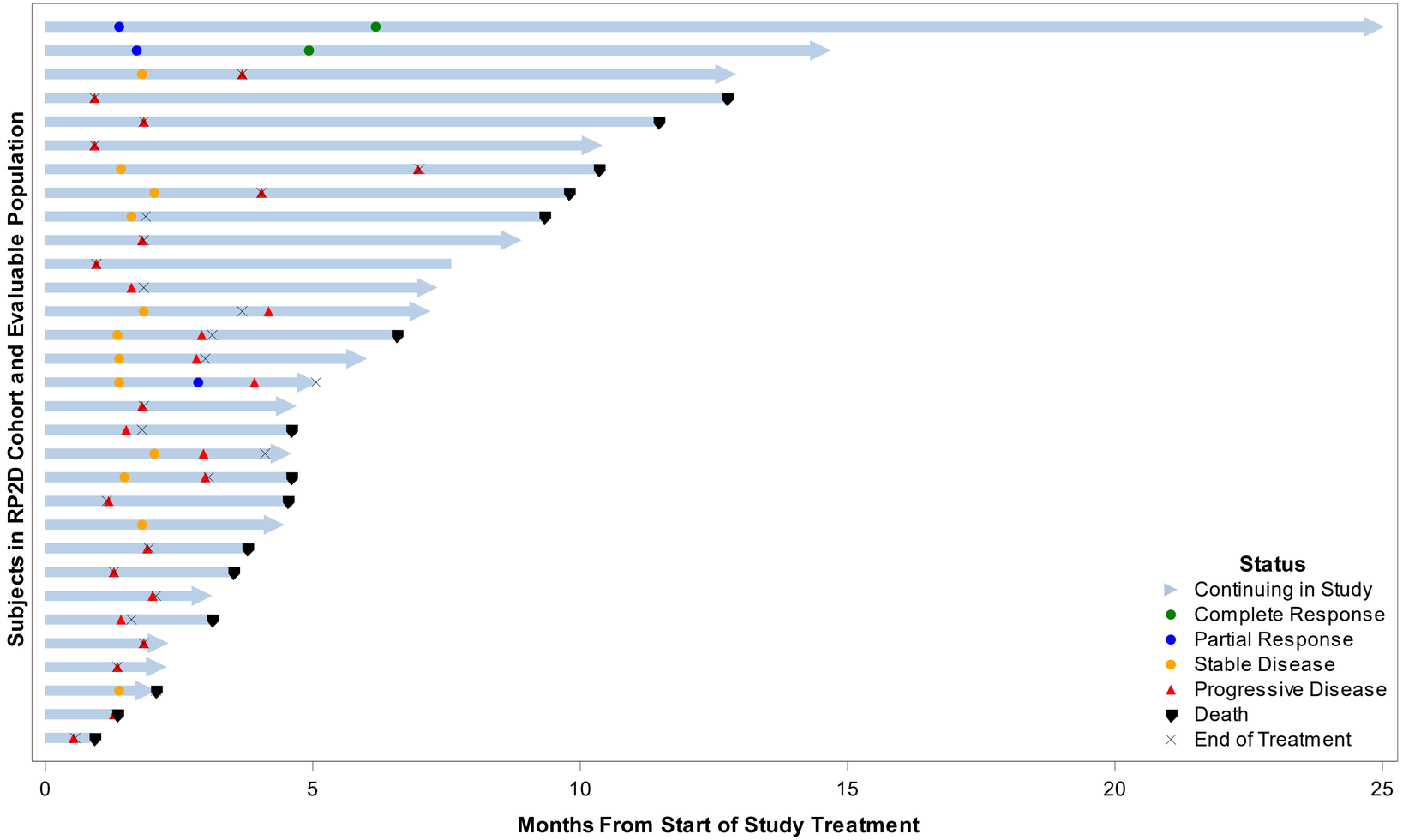
Schedule Escalation (Cohorts 7-9) and Expansion



- 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.

Presented By: Ravin Ratan, M.D. MD Anderson Cancer Center, Houston, TX, USA 04JUNE2021

Patient Overview: Swimmers Plot



Data cut: 16APR2021; Patients were considered evaluable for response if they completed 1-cycle of treatment and had 1-post baseline tumor assessments; continuing in study includes long-term follow-up (survival)

31 evaluable patients have been treated with TK216 +/- vincristine at RP2D for a median of 1.84 months, with a median follow-up of 4.6 months

Efficacy: Clinical Response Rates

	All Patients evaluable=54	Cohort 9 & Expansion (RP2D) evaluable=31
Overall Response Rate (ORR), n (%)	3 (5.6)	3 (9.7)
CR*, n (%)	2 (3.7)	2 (6.5)
PR**, n (%)	1 (1.9)	1 (3.2)
SD, n (%)	13 (24.1)	11 (35.5)
PD, n (%)	38 (70.4)	17 (54.8)
Disease Control Rate (DCR), n (%)	16 (29.6)	14 (45.2)
Median Duration of SD (95% CI)	1.8 (1.4, 3.7)	1.9 (1.4, 3.7)

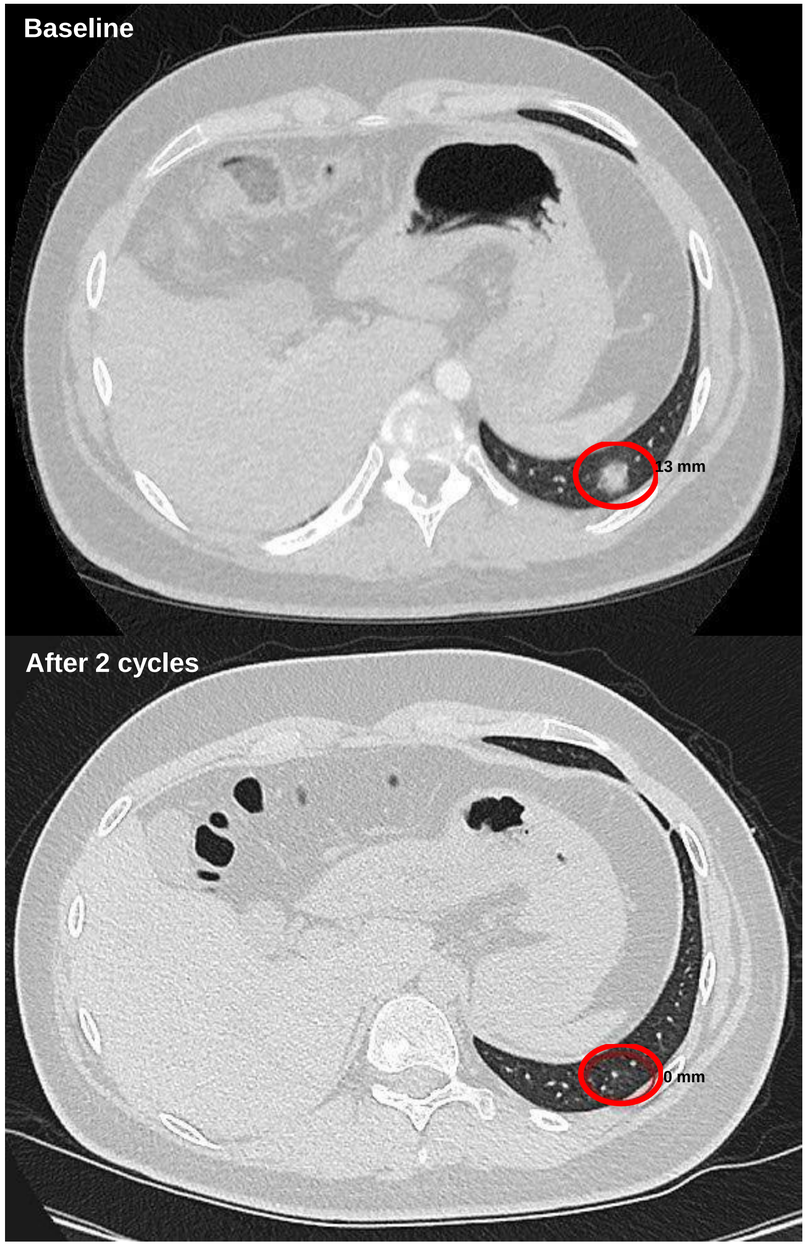
Data cut: 16APR2021; All patients- include Cohorts 1-8, Cohort 9 & Expansion; Patients were considered evaluable for response if they completed 1-cycle of treatment and had 1-post baseline tumor assessment; CR- complete response, PR- partial response, SD- stable disease, PD- progressive disease; ORR- number and percent of patients that achieved CR or PR; DCR- number of patients that achieved CR, PR or SD; * Two confirmed CRs with no PD at data cut; ** Unconfirmed PR observed in target lesion at Cycle 4 then PD observed at Cycle 6 in non-target lesions

Notable responses and disease control rates observed at the RP2D

Efficacy: Case Discussion (1/2)

Patient: 19-year-old male presented with Ewing sarcoma of the clavicle and multiple pulmonary metastases

- History:
  - Tumor genetics: EWSR1-FLI1 fusion
  - Prior 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 progressing lung metastases at study entry
- TK216 Treatment Course: TK216 200 mg/m^2/day for 14-28 days
  - Regression of all target lesions at Cycle 2 (PR)
  - Resection of residual non-target lung lesion at Cycle 6 (surgical CR)
  - Remains on treatment with TK216 + Vincristine >2 years since enrollment with no evidence of disease

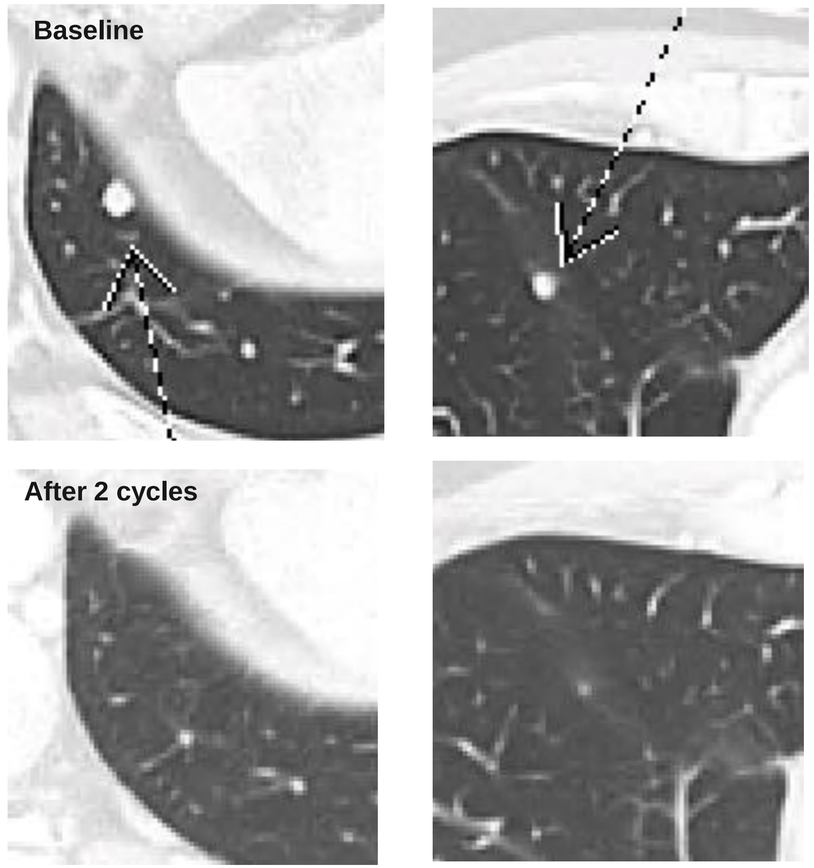


Sustained CR for >2 years in heavily pre-treated teenager with R/R Ewing sarcoma

Efficacy: Case Discussion (2/2)

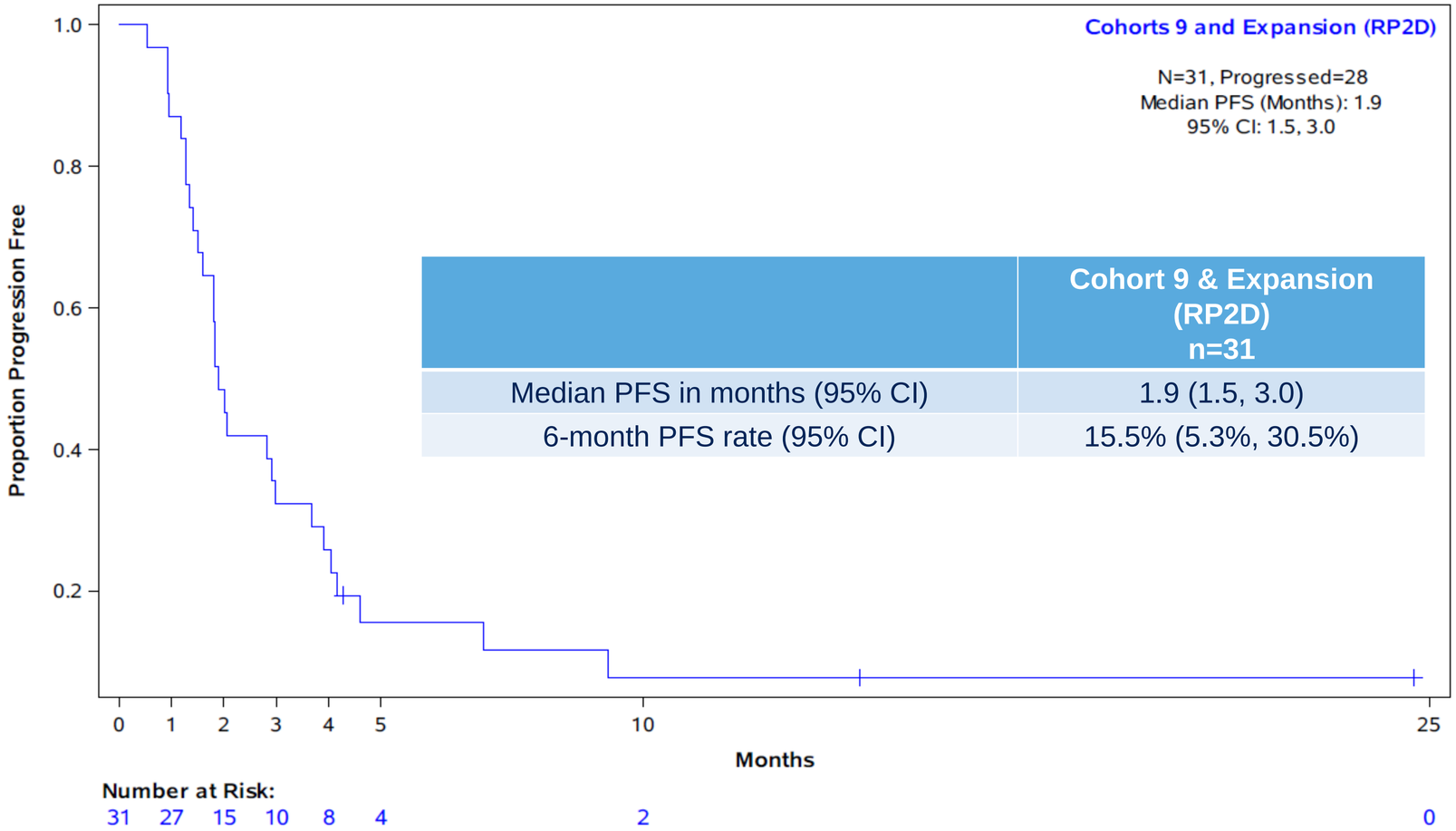
Patient: 51-year-old male presented with Ewing sarcoma of the kidney and multiple pulmonary metastases

- History:
  - Tumor genetics: EWSR1 translocation
  - Prior Therapy: VDC/IE, high-dose ifosfamide x1; surgical resection
  - Relapsed 1.6 years after initial diagnosis
  - Multiple progressing lung metastases at study entry
- TK216 Treatment Course: TK216 200 mg/m2/day for 14 + vincristine 0.75 mg/m^2 day 1
  - Regression of 90% of target lesions at Cycle 2 (PR)
  - Regression of all target lesions at Cycle 6 (CR)
  - Remains on treatment with TK216 monotherapy >1 year since enrollment with no evidence of disease



Sustained CR for >1 year in heavily pre-treated adult with R/R Ewing sarcoma

Efficacy: Progression-free Survival (PFS)



	Cohort 9 & Expansion (RP2D) n=31
Median PFS in months (95% CI)	1.9 (1.5, 3.0)
6-month PFS rate (95% CI)	15.5% (5.3%, 30.5%)

Data cut: 16APR2021; PFS is defined as time from enrollment to objective tumor progression via RECIST 1.1, or death from any cause, which ever occurs first; Evaluable patients were used for PFS analyses: defined as patients that completed 1-cycle of treatment and had 1-post baseline tumor assessments

Median PFS and 6-month PFS rate are consistent with observed disease control rates at RP2D

Summary

First in human study: Tk216 targets ETS family of oncoproteins

Phase 1 of study is complete and RP2D established

Efficacy at RP2D is encouraging

- 2 Complete responses are durable
- Good disease control: DCR = 45.2%

Safety profile is tolerable and manageable

- consisting of myelosuppression which is transient and reversible

Phase 2 currently enrolling