AACR 2013 Annual Meeting
April 9, 2013
Washington, DC

A Phase 1 Dose Escalation Study of TKM-080301, a RNAi Therapeutic Directed Against PLK1, in Patients With Advanced Solid Tumors

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Disclosure Information

AACR Annual Meeting 2013; April 9, 2013; Washington, DC

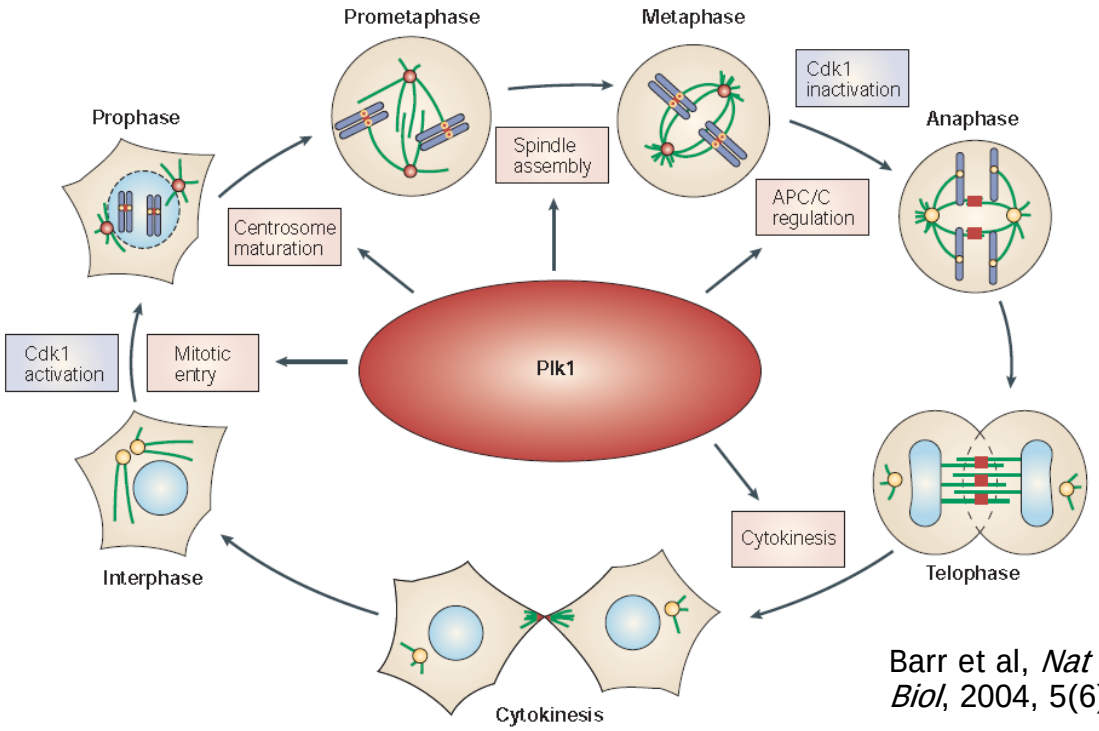
- I, Dr. Ramesh Ramanathan, have the following financial relationships to disclose:
  - Research Funding from Tekmira

-and-

- I will not discuss off label use and/or investigational use of marketed products in my presentation.

Polo-Like Kinase 1 (PLK1) as a Target

Key Roles in Cell Division



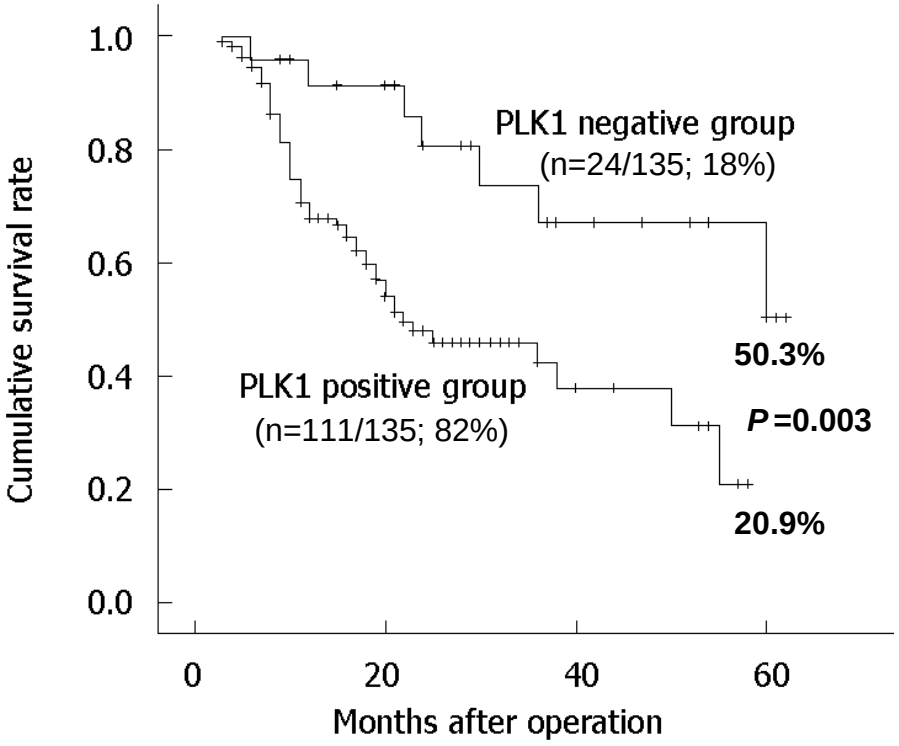
Barr et al, *Nat Rev Mol Cell Biol*, 2004, 5(6):429-440

- PLK1 is essential for multiple steps in cell division and DNA stability/repair
  - PLK1 knockout mouse is an embryonic lethal
- PLK1 has been shown to be over-expressed in many human tumors
  - Tumor cells depend on PLK1 activity more than non-transformed cells
- PLK1 gene silencing induces apoptosis and tumor cell death

PLK1 Tumor Expression

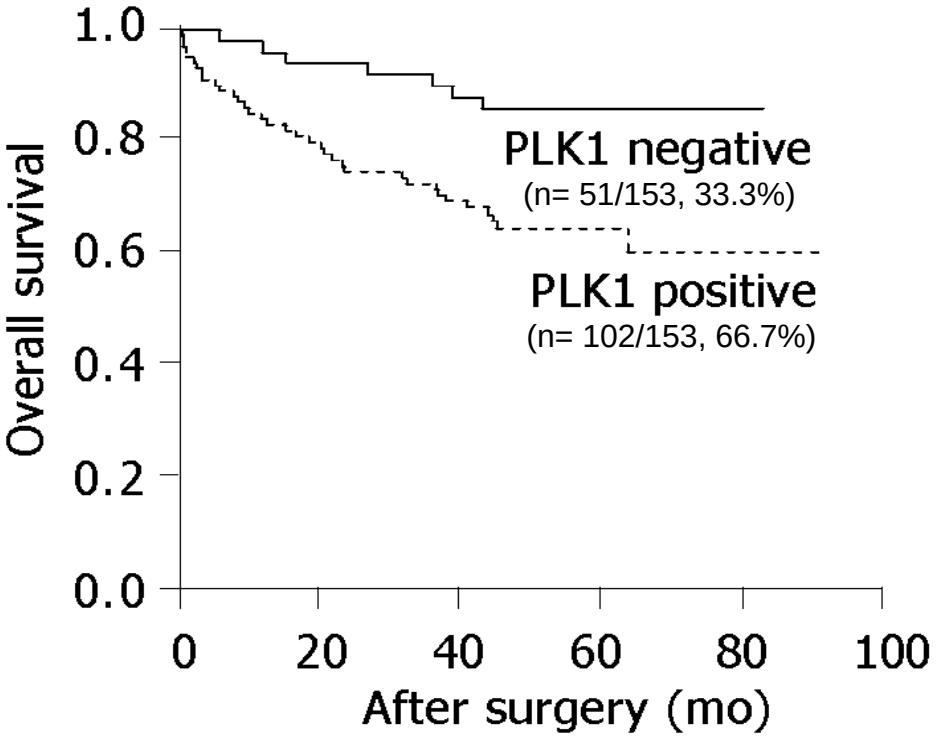
Correlates with Poor Clinical Outcomes

Hepatocellular Carcinoma



He *et al.,* .World J Gastroenterol, 2009

Colorectal Carcinoma

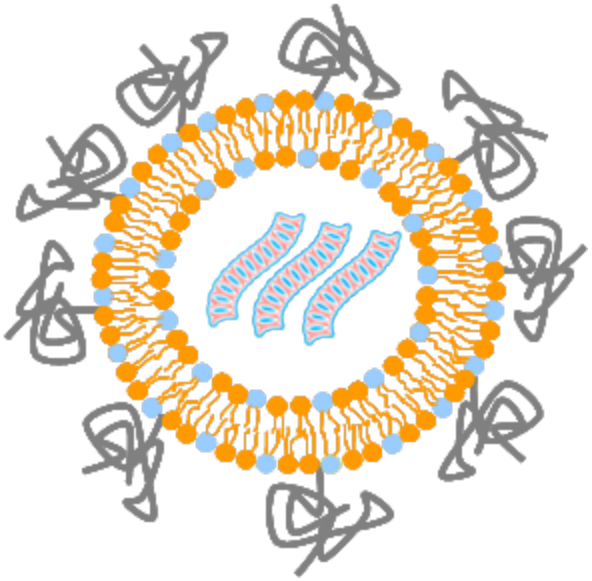


Weichert *et al,.* .World J Gastroenterol, 2005

TKM-080301

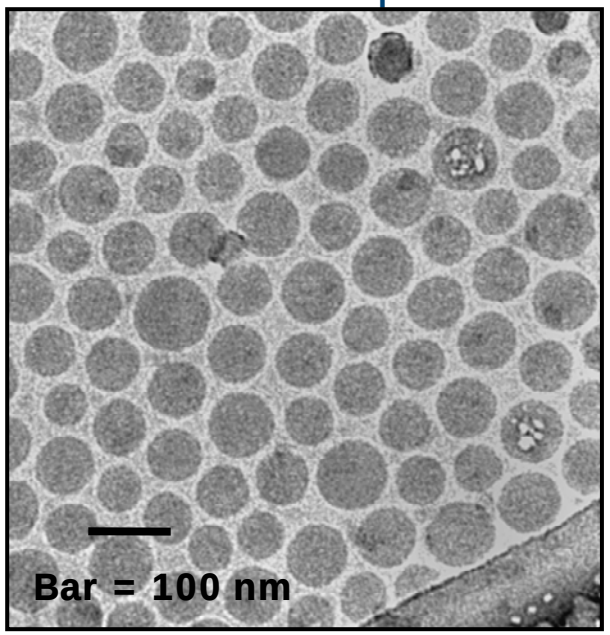
Lipid Nanoparticle (LNP) Formulation of PLK1 siRNA

LNP



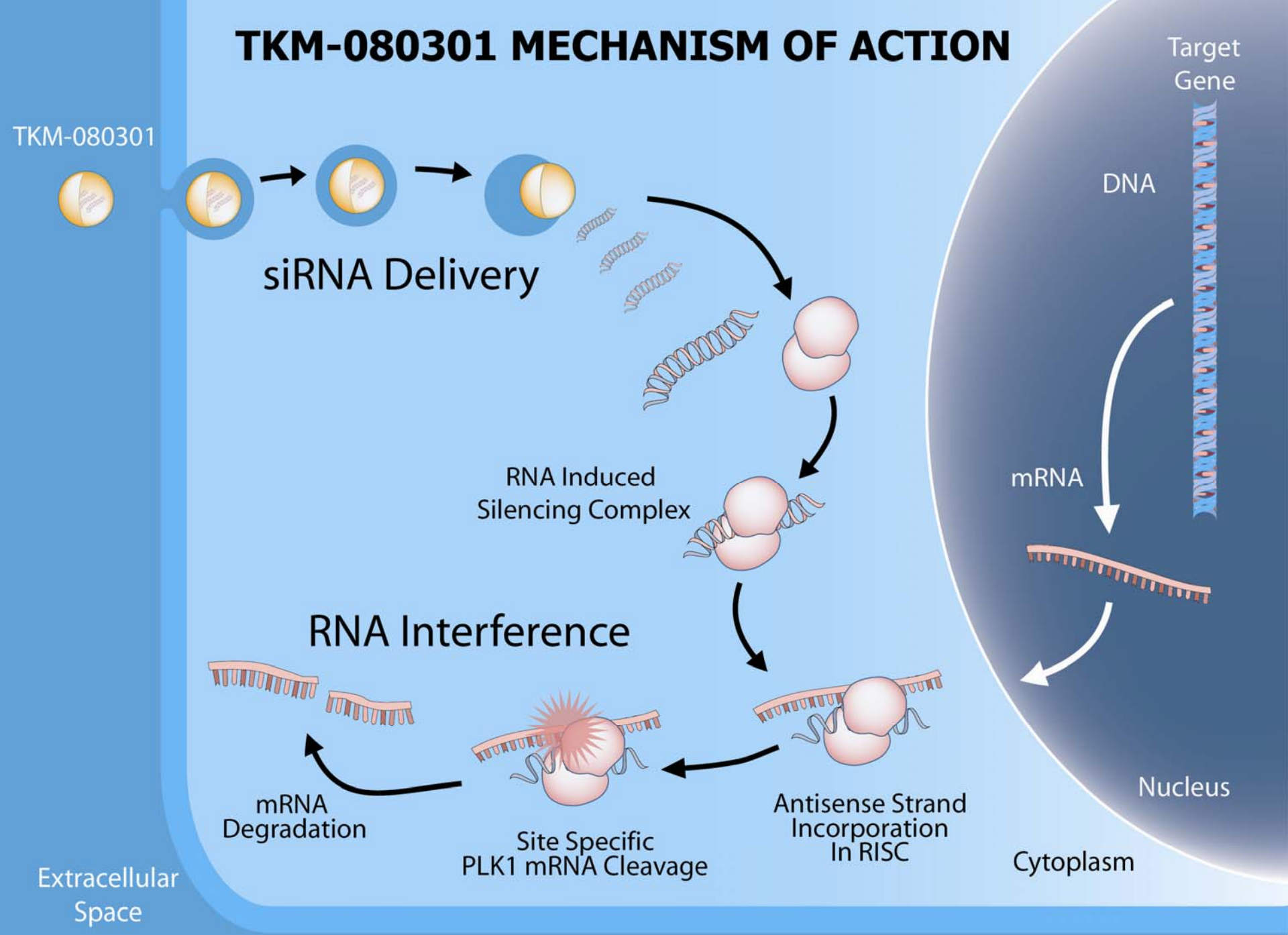
~80 nm diameter

Colloidal Dispersion



- LNP composition selected based on activity and circulation time
  - Formulation circulates ~3X longer than liver-directed LNP
- Mode of action distinct from small molecule PLK1 inhibitors
  - Highly selective for PLK1 mRNA sequence
  - Does not target other PLKs or other kinases
  - LNPs do not appreciably accumulate in bone marrow

TKM-080301 MECHANISM OF ACTION



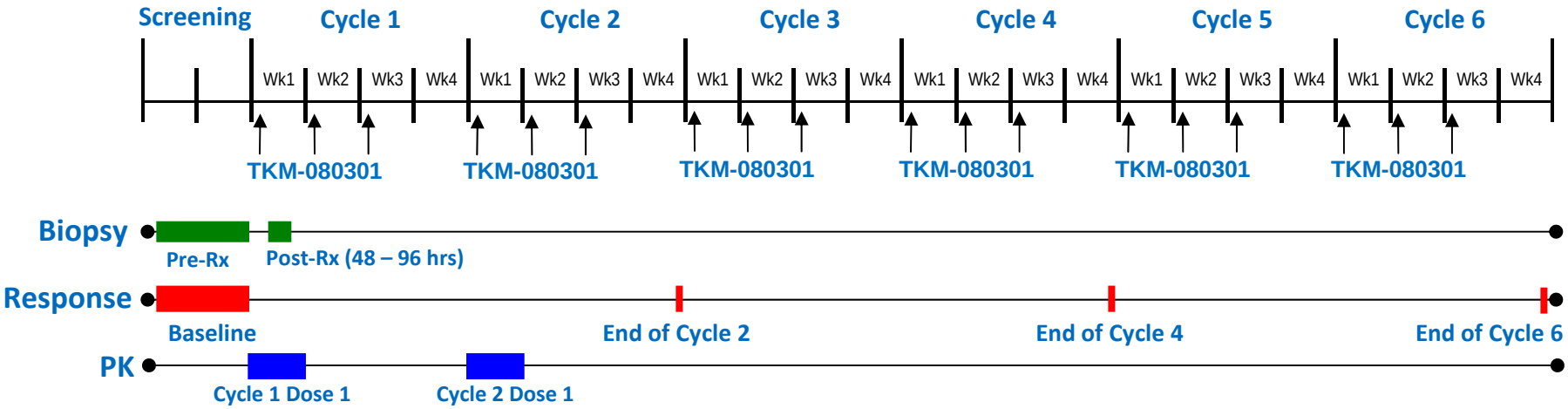
Study Objectives

NCT 01262235 - First-in-Human Study for TKM-080301

- Primary Objective:
  - Safety, tolerability, MTD determination
- Secondary Objectives:
  - Plasma pharmacokinetics
  - Anti-tumor activity
- Exploratory Objectives:
  - Pharmacodynamic measures including RNAi effects in pre- and post-dose biopsy samples

Basic Study Design

First-in-Human Study for TKM-080301



- Study Design:
  - Multi-center, 3+3 cohort dose-escalation (0.15 – 0.90 mg/kg)
  - Entry criteria typical for FIH trial in subjects with refractory cancer
  - Premeds included dexamethasone, acetaminophen, H1 and H2-blockade
  - TKM-080301 administered IV as 30-min. infusion weekly x 3 in 4 week cycles
  - Treatment may continue until disease progression
  - 10-subject Expansion Cohort at MTD planned & currently enrolling
- Reporting data on dose escalation only

Demographics and Baseline Characteristics

Dose Escalation Cohorts (0.15 to 0.9 mg/kg)

Characteristic	Result
Number of Subjects Enrolled	26 subjects
Median Age (Range)	62 yrs (35-79)
Gender	46% / 54% (M/F)
ECOG Performance Status of 0/1	62.5% / 37.5%
Mean No. of Prior Regimens (Range)	5.1 (1-14)
Tumor Types *Data as of March 1, 2013*	Colorectal (15) Neuroendocrine (2) Cholangiocarcinoma (2) Adrenocortical Carcinoma (2) Breast (1) Ovarian (1) Mesothelioma (1) Lung (1) Unspecified Adenocarcinoma (1)

Summary of Treatment Related Adverse Events

Dose Escalation Cohorts (0.15 to 0.9 mg/kg)

Dosing Summary	
Number of Subjects Treated	24
Total Doses of TKM-080301 Administered	152
Mean # of Doses per Patient (Range)	6.3 (1-31)

Most Frequent Adverse Events (All Grades)

Toxicity (N=24)	%[a]	Grade **1 & 2**	Grade **3 & 4**[b]
Rigors	33%	8	-
Fever	25%	6	-
Fatigue	17%	4	-
Altered Taste	17%	4	-
Headache	13%	3	-
Infusion Reaction	13%	2	1
Nausea	13%	3	-
Vomiting	8%	2	-
Diarrhea	8%	2	-

[a] AEs deemed study drug related in >5% of all treated subjects. [b]Other Grade 3 events in one subject each were hypoxia/dyspnea, thrombocytopenia and a non Q-wave MI.

Maximum Tolerated Dose Determination

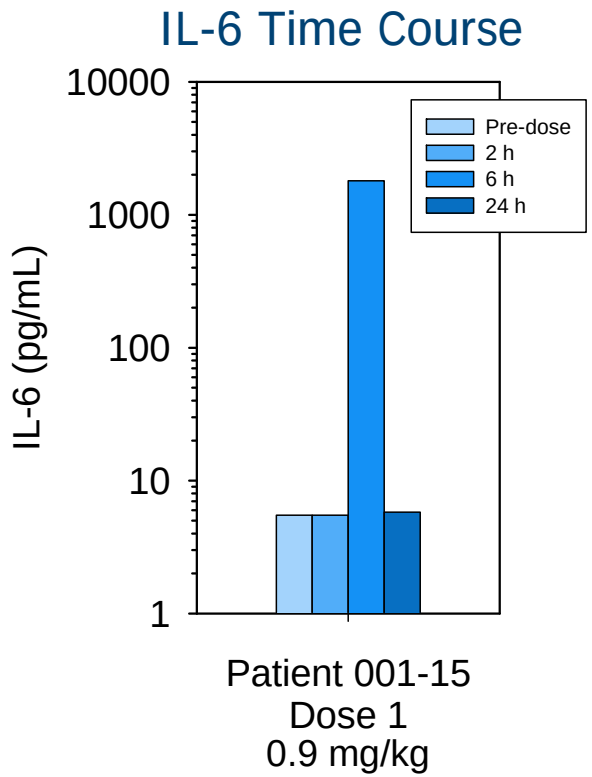
Dose (mg/kg)	Number of Subjects		DLTs
	Treated	Completed Cycle 1	
0.15	5	3	0
0.30	3	3	0
0.60	4	3	0
0.75	4	3	0
0.90/0.60[a]	8	4	2 Grade 3 thrombocytopenia Grade 3 hypoxia/dyspnea

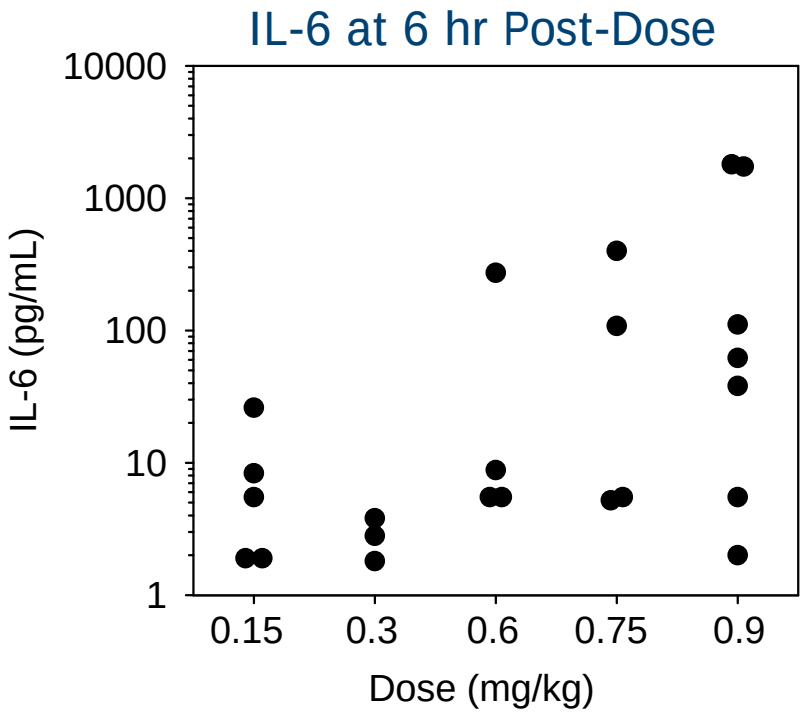
[a] Three subjects that received 0.9 mg/kg were reduced to 0.6 mg/kg

- Cytokine release symptoms (Grade 2/3) occurred at 0.9 mg/kg
  - Additional dexamethasone and diphenhydramine 3 hours after dosing
- Maximum Tolerated Dose estimated at 0.75 mg/kg
- Expansion Cohort being treated with 0.75 mg/kg

Inflammatory Biomarkers

Transient Cytokine Elevations at 6 Hours After Dosing

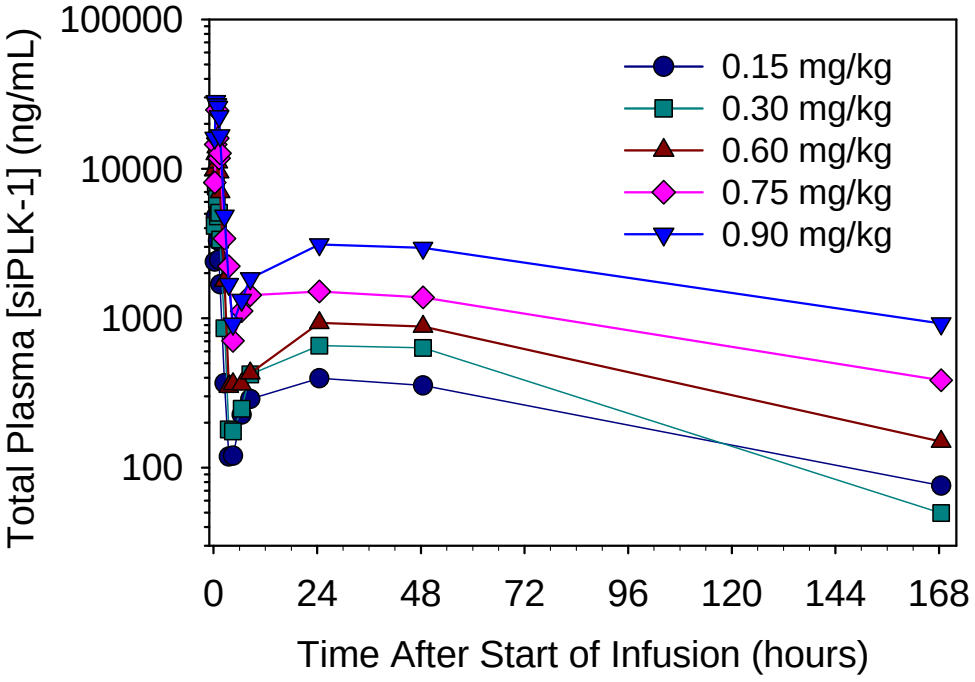




- Investigated a panel of 49 inflammatory biomarkers (pre-, 2, 6 & 24 h)
  - IL-6, MCP-1 and IL-8 were the only biomarkers that notably increased
- At doses <0.9 mg/kg, 4/16 (25%) of subjects had cytokine elevations that peaked at 6 hours and normalized by 24 hours
  - Cytokine release reactions were associated with peak levels
  - These reactions had a similar onset and response to treatment, without symptom recurrence or late sequelae

Pharmacokinetics

Cycle 1 – Mean Profiles



Cycle 1 – Mean Parameters

Dose (mg/kg)	n	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{½}$ (h)
0.15	5	4995	11989	52
0.30	3	8152	19593	38
0.60	4	16855	34743	52
0.75	4	26466	59759	71
0.90	7	28788	90290	68

Time points (from start of infusion): pre-dose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2.5, 3.5, 4.5, 6.5, 8.5, 24.5, 48.5, 168.5 hrs after Dose 1 of Cycle 1 and Cycle 2

- Plasma samples were analyzed using a validated capillary gel electrophoresis method
- Dose proportional C_{max} and AUC observed
- Similar profiles observed for cycles 1 and 2 with no accumulation between cycles

Clinical Anti-Tumor Activity

Dose Escalation Cohorts

- Extrapolated effective dosing range based on pre-clinical studies ≥ 0.60 mg/kg

	Doses < 0.6 mg/kg	Doses ≥ 0.6 mg/kg
# Treated	8	16
# Treated beyond Cycle 1	4	10
# Evaluable for Response	3	9
# with Clinical Benefit	0	4

- 4 of 9 (44%) evaluable subjects treated at ≥ 0.60 mg/kg had clinical benefit

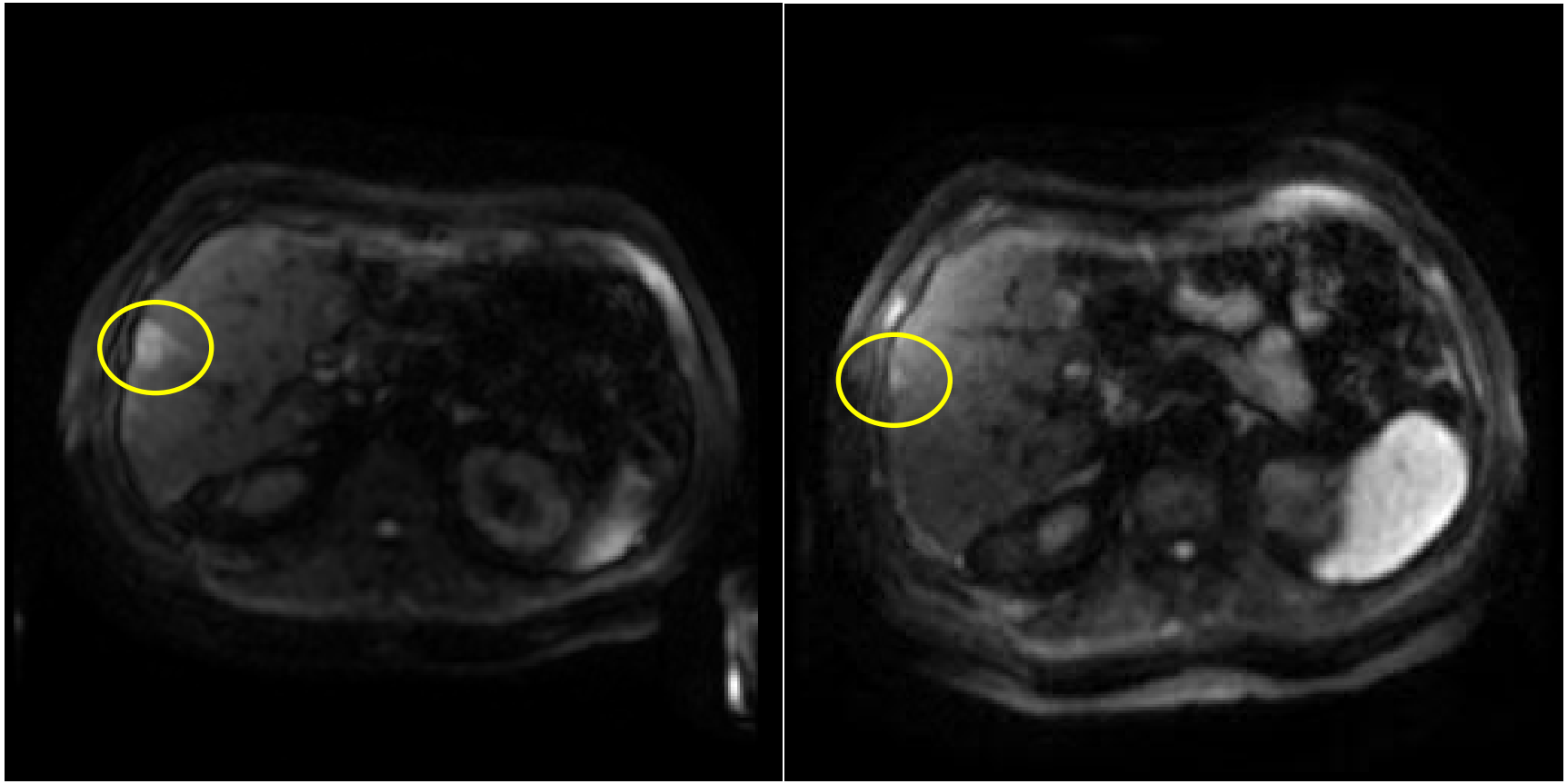
Subject	Dose	Tumor Type	# Prior Regimens	Best Response	Duration on Study
003-13	0.60	Colon	3	SD	6 mo.
003-20	0.90/0.60	NET	1	PR	11 mo.
003-24	0.75	NET	1	SD	4 mo.
002-25	0.75	ACC	3	SD	5.5 mo. (ongoing)

- Expansion cohort currently has 5 subjects treated; all too early to evaluate

Data as of March 1, 2013

Partial Response in Patient 003-20

64 y/o Male with Mid-gut Neuroendocrine Tumor (Appendiceal)



Baseline MRI 2/16/12

Pre-Treatment

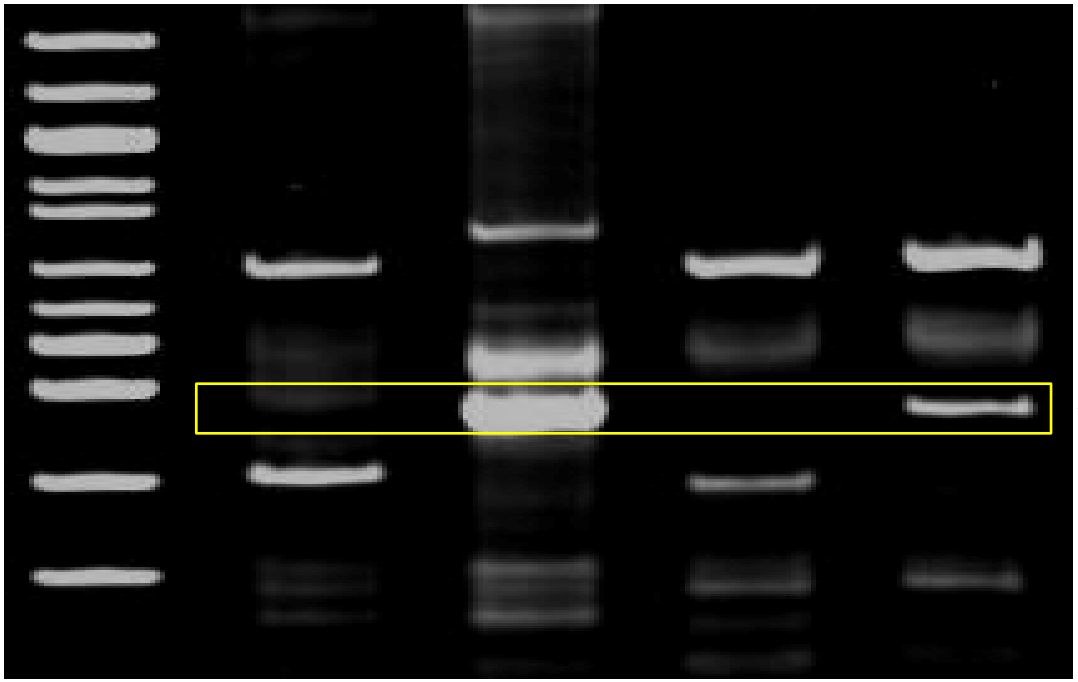
F/U MRI 4/30/12

End of Cycle 2

- PR observed at 1st evaluation (~2 months post therapy start) in NET
- Subject continued to have a PR after Cycles 4, 6, 8, and 10

Pharmacodynamic Evidence of RNAi

5' RACE PCR Identified Predicted PLK1 Cleavage Product Post-Treatment



Subject 002-26; colon; 0.75 mg/kg

Predicted 476-bp PLK1 mRNA cleavage product

- Biopsy samples collected pre-dose & 2 days after Dose 1 from the same lesion in the right lobe of liver
- Predicted cleavage product detected after TKM-080301 administration
- Results confirmed by sequencing

Summary and Next Steps

- Conclusions:
  - Phase 1 dose escalation complete and MTD estimated at 0.75 mg/kg
  - TKM-080301 generally well-tolerated in subjects dosed up to and including 0.75 mg/kg
    - Cytokine release symptoms were manageable, transient and without sequelae
  - Preliminary clinical benefit observed in 4 of 9 (44%) evaluable subjects at $\geq$ 0.60 mg/kg
  - RNAi effect confirmed in biopsy samples
- Next Steps:
  - Complete expansion cohort of 10 subjects at 0.75 mg/kg to confirm findings
  - Phase 2 in specific tumor types

Acknowledgements

- The subjects and families that participated in this study
- The study site personnel