

Phase I Study of Everolimus (RAD001) with Irinotecan and Cetuximab for 2nd line Treatment of Metastatic Colorectal Cancer: Hoosier Oncology Group GI05-102

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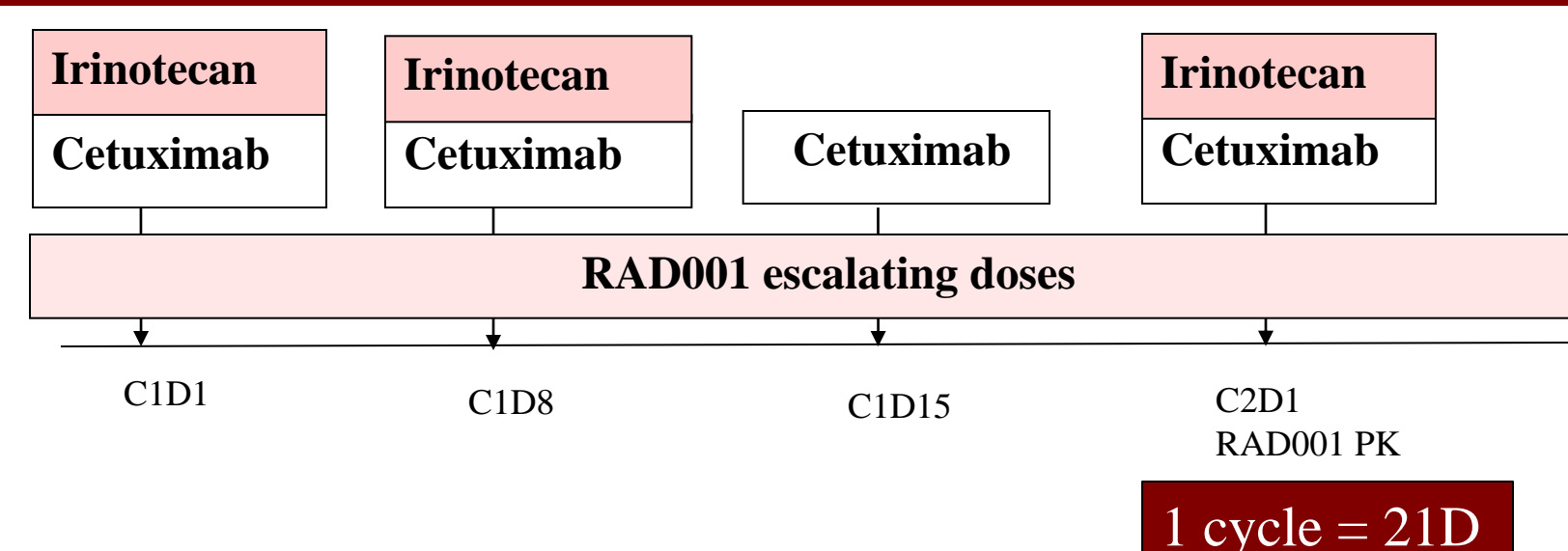
Background

- Cetuximab plus irinotecan is an effective 2nd-line option for pts with CRC (BOND, EPIC)
- Cetuximab is an anti-EGFR monoclonal antibody thought to be ineffective for patients with KRAS mut CRC based on retrospective analyses.
- PI3kinase/Akt/mTOR is one of the effector pathways modulated by Ras, thus mTOR inhibition could be effective when Ras overactive (ie KRAS mut)
- Preclinical studies show synergism between mTOR and EGFR inhibitors
- Hypothesis:** RAD001 is an oral mTOR inhibitor which could benefit KRAS WT CRC in combination with anti-EGFR therapy, and in KRAS mut CRC it could aid EGFR inhibitors overcome resistance.

Objectives

- Primary:** - Safety and tolerability, MTD
- Secondary:** - Trough PK for RAD001; PD markers; - preliminary efficacy: RR, PFS, OS

Methods: Study Schema



Dose Level	RAD001	Irinotecan	Cetuximab*
Cohort 1	5 mg QOD	125 mg/m ² D1, 8	250 mg/m ² D1, 8, 15
Cohort 2	5 mg QD	125 mg/m ² D1, 8	250 mg/m ² D1, 8, 15
Cohort 3	10 mg QD	125 mg/m ² D1, 8	250 mg/m ² D1, 8, 15

*Cetuximab 400 mg/m² loading, then 250 mg/m² IV weekly

Methods: Clinical

Eligibility Criteria

- Age ≥ 18 years old
- UGT1A1 *28 7/7 genotype not present
- ECOG performance status 0 to 2
- Metastatic colorectal cancer which progressed after first line chemotherapy +/- bevacizumab
- No other active malignancies
- No symptomatic brain metastasis
- DLT: during cycle 1 (21 days):**
 - Gr3/4 febrile neutropenia, Gr 4 Plt > 4 days, Gr 4 ANC > 7days
 - Gr 3/4 non-heme toxicity if in excess of stopping rules
 - Missed > 14 days of therapy for toxicity

Results: Clinical

Table 1. Patients' characteristics (n=30)

Characteristic	No.	%
Male/Female	16/14	53/47
Caucasian/African American/Asian	26/3/1	87/10/3
Median Age (range) yrs	60.5 (25-77)	
ECOG PS 0/1	20/10	
Prior therapies	30	100
oxaliplatin based	29	97
irinotecan based	1	3%
Cycles	Median 2 (1-34)	
KRAS Wild/NA	12/15/3	40/50/10

Table 2. Dose levels and DLTs* (n=30)

Cohort	RAD001	#DLTs	DLT	# Cycles median (range)
1* (n=9)	5 mg QOD	2	Gr3 Diarrhea Gr3 Febrile Neutropenia	2 (1-34)
1 (n=3)	5 mg QOD	0	-	6 (2-10)
2 (n=4)	5 mg QD	0	-	5 (1-13)
3 (n=4)	10 mg QD	2	Gr3 Mucositis	2 (2-6)
2 MTD expansion (n=10)	5 mg QD	1	Gr 3 Mucositis	3.5 (1-18)

*The study was amended after the first 9 pts enrolled, to include **stopping rules** for excessive toxicity ≥ Grade 3 beyond what was expected with Irinotecan and Cetuximab: for diarrhea (>30%), nausea/vomiting (>15%), febrile neutropenia (>15%) and acne-skin rash (>20%).

**MTD= RAD001 po 5 mg QD
Irinotecan 125 mg/m² QW x 2/3
Cetuximab 250 mg/m² QW**

Reasons for Treatment Discontinuation

- Disease progression n=13
- Adverse events n=8
- Patient decision n=2
- Patient non-compliance n=1
- Physician decision n=1 (symptom deterioration)

Results: Toxicity

Table 3. Most Common Treatment-Emergent AEs

Cohort	Adverse Event	All grades	Gr 3
1* (n=12)	Diarrhea	9	4
	Rash/acne	9	2
	Nausea	9	1
	Fatigue	8	0
	Anorexia	8	0
	Vomiting	8	0
	ANC	6	3 / 1 Gr 4
	Mucositis	6	0
	Alopecia	5	0
	Fatigue	11	3
	Nausea	10	2
	2 (n=14)	Diarrhea	9
Rash/acne		9	3
Anorexia		8	1
Alopecia		8	0
Mucositis		6	2
Vomiting		6	2
Hemoglobin		6	0
Leukocytes		5	0
Magnesium		5	0
ANC		5	0
3 (n=4)	Mucositis	4	2
	Anorexia	3	1
	Diarrhea	3	1
	Fever	3	0
	Hemoglobin	3	0
All (n=30)	Rash/acne	3	0
	Diarrhea	21	9
	Rash/acne	21	5
	Fatigue	20	3
	Nausea	20	3
	Anorexia	19	2
	Mucositis	16	4
	Alopecia	15	0
	Vomiting	15	2
	ANC	12	3 / 1 Gr 4
	Hemoglobin	12	1

Results: Pharmacokinetics/Pharmacodynamics

Table 4: PK for RAD001 at steady state (C2D1)

RAD001 dose	n	RAD001	RAD001 historical*
		Mean C _{min} ± SD (ng/mL)	Mean C _{min} ± SD (ng/mL)
5 mg QOD	4	8.55 ± 4.71	n/a
5 mg QD	5	8.5 ± 5.96	5.4 ± 1.8
10 mg QD	1	9.6	13.2 ± 7.9

*O'Donnell A, JCO 2008

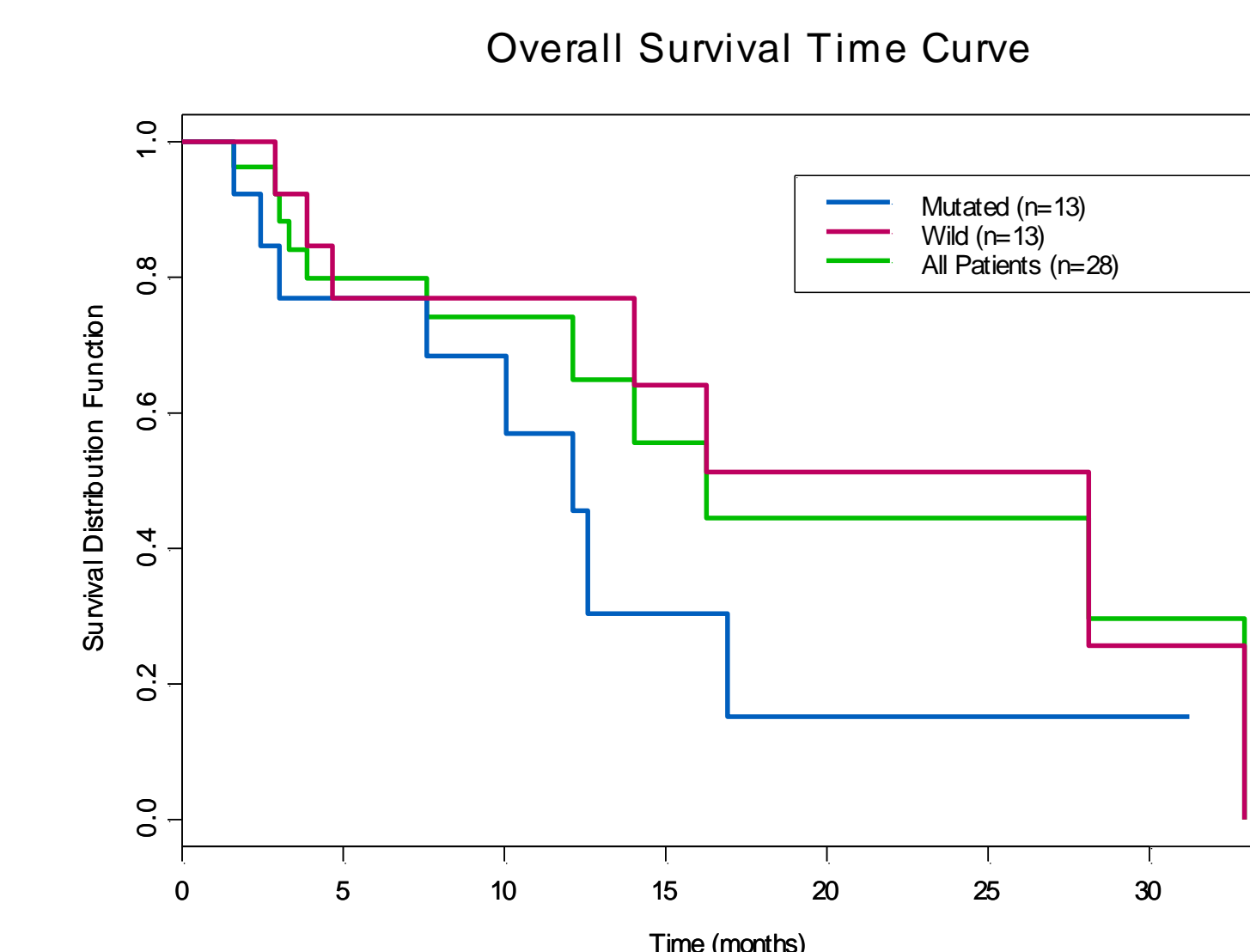
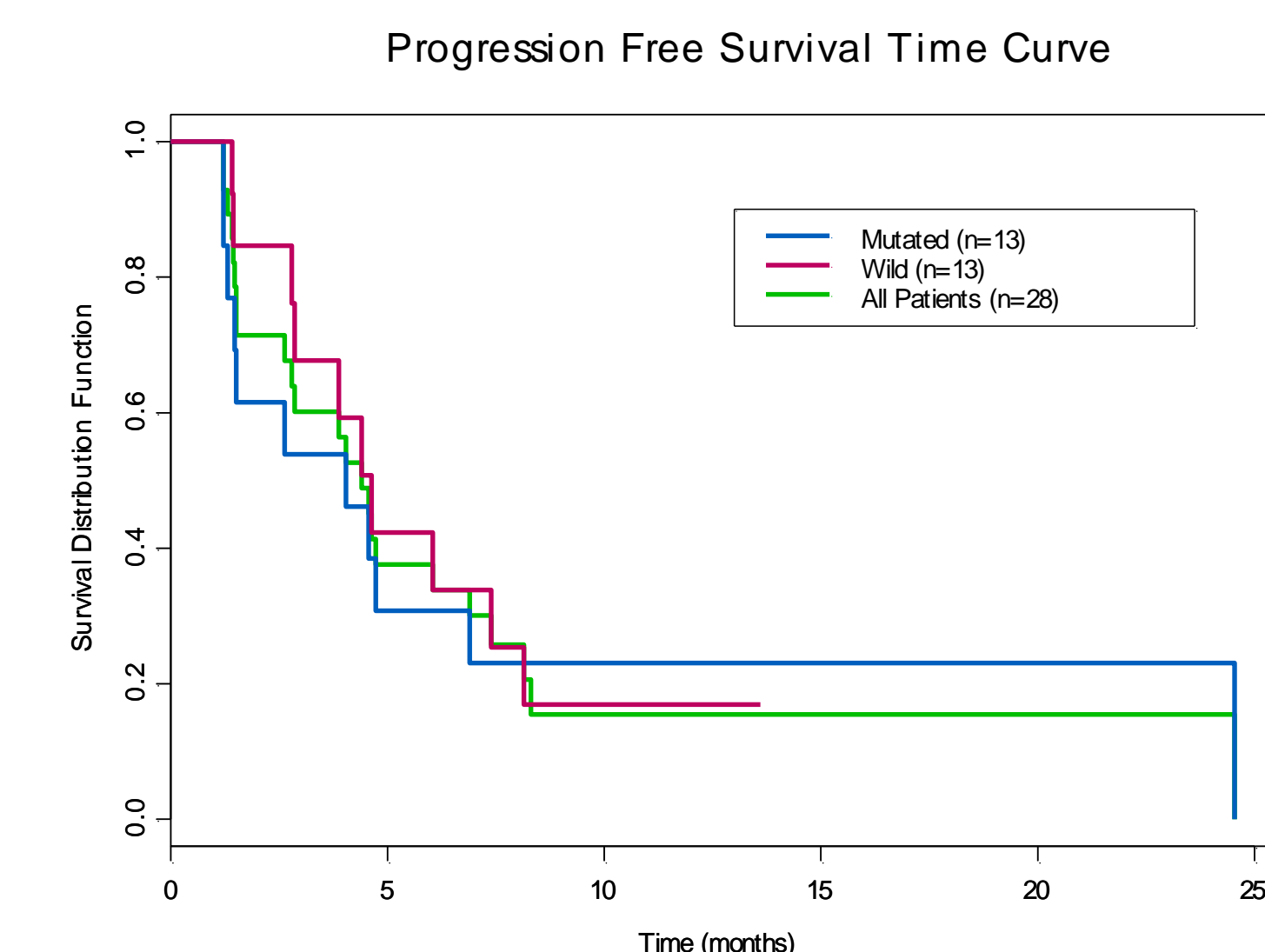
- 1/18 EGFR gene ratio 4.45 (amplified) vs 1 (non-amplified)
- 2/15 BRAF mutated (V600E, D594G) vs WT
- 4/13 PI3K mutated or amplified vs WT
- 6/11 PTEN low (H-score 0-10) vs normal
- 5/12 pS6 low (H-score ≤ 50) vs high (H-score > 50)
- 1/16 pAkt high (H-score >50) vs low (H-score ≤ 50)

* H-score = 1x(% cells +1 intensity) + 2x(% cells +2 intensity) + 3x(% cells +3 intensity)

Results: Antitumor Efficacy

Tumor type	Response	Median PFS (95% CI)	Median OS (95% CI)
Overall	1 CR / 4PR 10 SD 13 PD	4.40 months (2.63-6.90)	14.03 months (7.59-28.12)
KRAS WT	1 CR / 2 PR 4 SD 6 PD	4.63 months (2.79-8.15)	28.12 months (4.67-32.95)
KRAS MUT	1 PR 6 SD 6 PD	4.04 months (1.31-6.90)	12.12 months (3.02-16.92)
PI3K WT	2 PR / 4SD 7 PD	3.88 months (1.48-6.90)	12.58 months (3.88-28.12)
PI3K MUT	2 SD 1 PD	4.04 months (1.22-7.39)	16.92 months (12.12-n/a)
PTEN low	1 PR / 2 SD 2 PD	7.39 months (1.22-8.31)	n/a (1.69-n/a)
PTEN normal	1 PR / 4 SD 6 PD	3.88 months (1.45-4.57)	12.58 months (3.88-16.92)
pS6 low	1 PR / 1 SD 2 PD	6.01 months (1.22-8.31)	12.12 (3.88-n/a)
pS6 high	1 PR / 5 SD 6 PD	3.45 months (1.45-6.90)	16.26 months (2.89-28.12)

Results:



Conclusions

- MTD is RAD001 5 mg orally daily with Irinotecan 125 mg/m² QW x 2/3 and Cetuximab 250 mg/m² QW**
- Most common toxicities were gastrointestinal, rash, fatigue and mucositis
- PK: RAD001 C_{min} at steady state is similar with that seen with single agent RAD001, suggesting no drug-drug interaction with irinotecan/cetuximab
- Encouraging OS for 2nd line KRAS wild type CRC
- Phase II trial ongoing through the HOG in KRAS WT and mutated CRC

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