Regorafenib Dose Optimization Study (ReDOS): A randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC)—An ACCRU Network study

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Background

- ReDOS is a randomized Phase II study of a lower starting dose with planned dose escalation of regorafenib compared to the standard dose in patients with refractory mCRC
- Regorafenib has been shown to improve overall survival (OS) in CORRECT[1] and CONCUR[2] trials for patients with mCRC
- Toxicities such as hand-foot skin reaction (HFSR, commonly occurring during the first 2 weeks) and fatigue may limit its use
- There is a need to optimize the dose of Regorafenib in patients with refractory mCRC to allow maintenance of the observed anti-tumor benefits while improving the tolerability profile

Methods

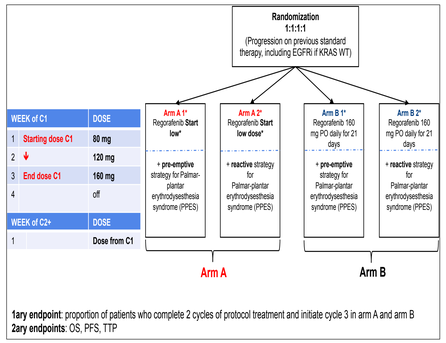
A randomized phase II US based study through the ACCRU (Academic and Community Cancer Research United) research network of regorafenib dose-escalation (Arm A: 80 mg/day, weekly dose escalation if no significant drug-related toxicities, up to 160 mg/day) vs. standard dose (Arm B: 160 mg/day) in patients (pts) with mCRC for 21 days of a 28-day cycle. Pts were randomized 1:1:1:1 to arms A1 and B1 (Pre-emptive Clobetasol for PPES); A2 and B2 (Reactive Clobetasol).

Primary endpoint: proportion of patients who complete 2 cycles of treatment and initiate Cycle 3

Assuming an 8-week planned continuation rate of 45% in the control (Arm B) group, and desiring an improvement to 63% (+18%) in the experimental (Arm A) group, a one-sided test with alpha = 0.20 and power of 80% will require a sample size of 110 patients enrolled to both arms

Analyses will be modified intent-to-treat (mITT)
Pts are evaluable for primary endpoint if eligible, consented, received any protocol treatment.
A Fisher's Exact Test will be used to detect a difference in 8-week planned continuation rates between treatment strategies with 95% confidence intervals

Study Design



1ary endpoint: proportion of patients who complete 2 cycles of protocol treatment and initiate cycle 3 in arm A and arm B
2ary endpoints: OS, PFS, TTP

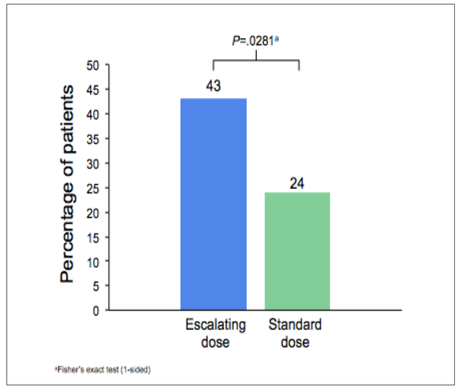
Results

Patient demographics

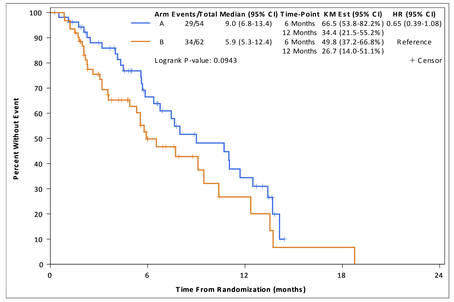
Characteristic	Arm A (N=54)	Arm B (N=62)	Total (N=116)	P value
Age				
Median (Q1, Q3)	62 (53, 68)	61 (53, 68)	61 (53, 68)	0.9010
Gender				
Female	18 (33.3%)	27 (43.5%)	45 (38.8%)	
Male	36 (66.7%)	35 (56.5%)	71 (61.2%)	0.2601
PS				
0	20 (37.0%)	23 (37.1%)	43 (37.1%)	
1	34 (63.0%)	39 (62.9%)	73 (62.9%)	0.9947
Primary Tumor Status				
Local recurrence	4 (7.4%)	1 (1.6%)	5 (4.3%)	
Resected	37 (68.5%)	44 (71.0%)	81 (69.8%)	
Unresected	13 (24.1%)	17 (27.4%)	30 (25.9%)	0.3015
Number of Metastatic Sites				
1	6 (11.1%)	2 (3.2%)	8 (6.9%)	
2	12 (22.2%)	18 (29.0%)	30 (25.9%)	
3+	36 (66.7%)	42 (67.7%)	78 (67.2%)	0.2096
BRAF Results*				
Mutated	1 (1.9%)	2 (3.2%)	3 (2.6%)	
Wild Type	15 (27.8%)	20 (32.3%)	35 (30.2%)	0.7485
KRAS Results*				
Mutated	21 (38.9%)	33 (53.2%)	54 (46.6%)	
Wild Type	27 (50.0%)	24 (38.7%)	51 (44.0%)	0.1486

* Unknown: 67% (BRAF) and 9% (KRAS)

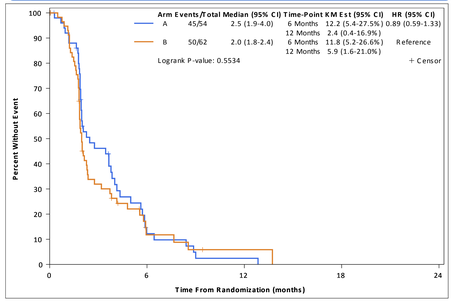
Primary Endpoint: % of Patients Starting Cycle 3



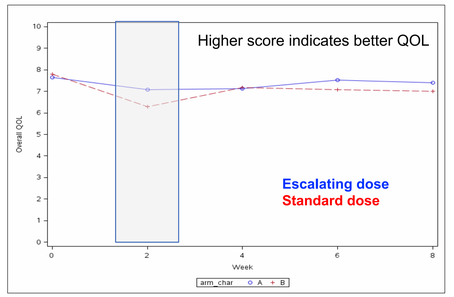
Overall Survival



Progression Free Survival



Overall Quality Of Life (QOL)



Reasons For End of Treatment

	Arm A (N=54)	Arm B (N=62)	Total (N=116)	P-value
End of Treatment Reasons				0.7559c
AEs/Side Effects/Complications	10 (18.5%)	6 (9.7%)	16 (13.8%)	
Alternative Therapy	1 (1.9%)	2 (3.2%)	3 (2.6%)	
Death On Study	1 (1.9%)	2 (3.2%)	3 (2.6%)	
Disease Progression, Relapse during active treatment (Intervention)	33 (61.1%)	36 (58.1%)	69 (59.5%)	
Other	2 (3.7%)	2 (3.2%)	4 (3.4%)	
Patient Off-Treatment (Intervention) for other complicating disease	2 (3.7%)	2 (3.2%)	4 (3.4%)	
Patient withdrawal/Refusal after beginning therapy (Intervention)	2 (3.7%)	4 (6.5%)	6 (5.2%)	
Still receiving treatment	3 (5.6%)	8 (12.9%)	11 (9.5%)	

cChi-Square

Weekly Dose Intensity during C1 and C2

	Cycle 1		Cycle 2	
	Arm A (N=54)	Arm B (N=62)	Arm A (N=41)	Arm B (N=47)
Week 1				
Percentage of planned dose received				
Mean (SD)	98.3 (6.9)	95.6 (14.2)	99.6 (2.3)	78.0 (31.0)
Median (Range)	100.0 (57.1, 107.1)	100.0 (25.0, 100.0)	100.0 (85.7, 100.0)	100.0 (0.0, 100.0)
Dose received				
Mean (SD)	78.6 (5.5)	153.0 (22.7)	128.7 (37.2)	124.7 (49.5)
Median (Range)	80.0 (45.7, 85.7)	160.0 (40.0, 160.0)	160.0 (40.0, 160.0)	160.0 (0.0, 160.0)
Omission	5 (9.3%)	8 (12.9%)	1 (2.4%)	7 (14.9%)
Delayed	1 (1.9%)	1 (1.6%)	0	6 (12.8%)
Week 2				
Percentage of planned dose received				
Mean (SD)	83.6 (30.8)	86.9 (27.7)	95.1 (20.0)	76.7 (32.5)
Median (Range)	100.0 (0.0, 104.8)	100.0 (0.0, 100.0)	100.0 (0.0, 133.3)	87.5 (0.0, 100.0)
Dose received				
Mean (SD)	100.3 (37.0)	139.1 (44.3)	124.6 (45.3)	122.7 (52.0)
Median (Range)	120.0 (0.0, 125.7)	160.0 (0.0, 160.0)	160.0 (0.0, 160.0)	140.0 (0.0, 160.0)
Omission	12 (22.2%)	12 (19.4%)	5 (12.2%)	10 (21.3%)
Delayed	1 (1.9%)	0	0	2 (4.3%)
Week 3				
Percentage of planned dose received				
Mean (SD)	60.3 (44.2)	68.2 (42.2)	84.8 (35.9)	69.9 (38.7)
Median (Range)	85.7 (0.0, 100.0)	100.0 (0.0, 100.0)	100.0 (0.0, 133.3)	75.0 (0.0, 100.0)
Dose received				
Mean (SD)	96.4 (70.7)	109.0 (67.5)	112.1 (56.3)	111.9 (61.9)
Median (Range)	137.1 (0.0, 160.0)	160.0 (0.0, 160.0)	120.0 (0.0, 160.0)	120.0 (0.0, 160.0)
Omission	19 (35.2%)	23 (37.1%)	9 (22.0%)	10 (21.3%)
Delayed	3 (5.6%)	0	0	1 (2.1%)

AEs Occurring in ≥4% of Patients

n (%)	Escalating dose (n=54)		Standard dose (n=62)	
	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	7 (13.0)	0	11 (17.7)	0
Hand-foot skin reaction (HFSR)	8 (14.8)	0	10 (16.1)	0
Abdominal pain	9 (16.7)	0	4 (6.5)	0
Hypertension (HTN)	4 (7.4)	0	9 (14.5)	0
Hyponatremia	2 (3.7)	1 (1.9)	4 (6.5)	1 (1.6)
Bilirubin increased	2 (3.7)	0	5 (8.1)	0
Alkaline phosphatase increased	3 (5.6)	0	1 (1.6)	1 (1.6)
AST increased	1 (1.9)	0	4 (6.5)	0
Dehydration	0	0	5 (8.1)	0
Dyspnea	1 (1.9)	1 (1.9)	3 (4.8)	0
Lymphoctye count decreased	4 (7.4)	0	0	0
Maculopapular rash	0	0	3 (4.8)	0

Summary

Baseline Demographics	
Time period	June 2015-June 2017
N	116 evaluable (A=54, B=62)
Median age	61 (range 29-81)
Male/Female	61/39%
ECOG PS 0/1	37/63%
KRAS MT/WT/ UNK	47/44/9%

	Arm A n=54	Arm B n=62	*P*-Value
Primary Endpoint, patients initiating 3rd cycle	**43%**	**24%**	**0.028**
mOS (mos)	9	5.9	0.094
mPFS (mos)	2.5	2.0	0.553
% HFSR	15%	16%	n/a
% HTN	7%	15%	n/a
% Fatigue	13%	18%	n/a

Conclusions

- A strategy with weekly dose escalation of regorafenib from 80 mg to 160 mg/day was found to be superior to a starting dose of 160 mg/day.
- A trend for improved OS was seen in the dose escalation arm.
- At 2-wks from initiation of therapy, the dose escalation strategy did not appear to compromise QOL unlike the standard dose administration.
- **These results potentially establish a new standard for optimizing regorafenib dosing through a dose escalation strategy**.
- Further data on outcomes of preemptive vs. reactive clobetasol strategies and PK analysis is will be presented at a later meeting.

ACCRU (Academic and Community Cancer Research United)

1. Grothey A et al. *Lancet.* 2013;381:303-312.
2. Li J et al. *Lancet Oncol.* 2015;16(6):619-629