Chemoradiation (CRT) Safety Analysis of ACOSOG Z6041: A Phase II Trial of Neoadjuvant CRT followed by Local Excision in uT2 Rectal Cancer

Emily Chan, Qian Shi, Julio Garcia-Aguilar, Peter Cataldo, Jorge Marcet, David Medich, Alessio Pigazzi, Samuel Oommen, Bruce G. Wolff, Craig S. Johnson, Bridget Sanders, Xiomara Carrero, Mitchell C. Posner, David M. Ota, and Charles R. Thomas, Jr.

Background

Radical surgery of rectal cancer results in significant morbidity.

Sphincter-sparing approaches, such as local excision (LE), result in less morbidity but yield a higher local recurrence rate.

ACOSOG Z6041 explored neoadjuvant chemoradiation followed by LE for uT2 rectal cancer.

Objectives

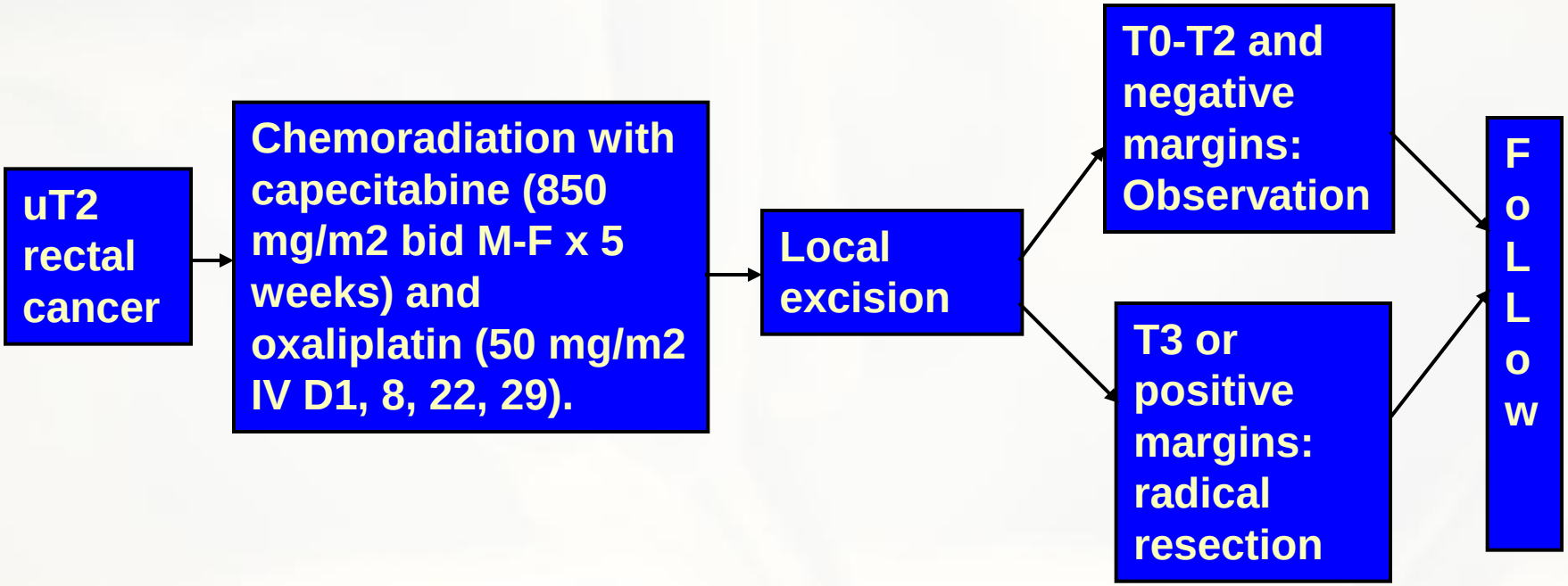
Overall Study Primary Objective:

- **3 yr DFS in uT2N0 rectal cancer**

Specific aim of the present analysis:

- **To report the toxicity results from neoadjuvant chemoradiotherapy**

Study Design



Radiation Therapy Protocol

External beam radiation therapy (EBRT) with megavoltage linear accelerators (≥ 6 MV) was delivered to a 3-4 field pelvis arrangement following CT-based simulation and computer-assisted treatment planning

Intensity-modulated radiotherapy (IMRT) was allowed after a protocol modification, primarily to increase accrual.

Details on IMRT guidelines can be found in the protocol document at http://www.acosog.org or www.qarc.org

Patients were treated 5 days/week at 1.8 Gy/day for 25 fractions to a dose of 45 Gy to PTV1, followed by a three-fraction boost to PTV2 (defined as GTV plus 2 cm) for a total dose of 54 Gy.

Following observation of an unfavorable toxicity profile EBRT dose was reduced from 54 to 50.4 Gy.

All fields were treated daily.

Radiation Therapy QARC Review

Of 90 pts, 80 pts rec'd conformal non-IMRT RT, 10 pts - IMRT

Intensity-modulated radiotherapy (IMRT) was allowed after a protocol modification, primarily to increase accrual.

At the time of this analysis, 80 pts had undergone treatment reviews

71 of 80 pts were full Evaluable, with 62 of 71 having doses and volumes consistent with the protocol.

8 cases were scored as Unevaluable due to QARC benchmark requirements not being submitted. These 8 cases do have doses & volumes consistent with the protocol.

No Major Deviations,

10 Minor Deviations, including 9 dose deviations & 1 both dose & volume deviation

13 Unevaluable cases, including 9 without required QARC benchmark submission & 4 with incomplete data submission

Eligibility Criteria

ECOG PS ≤ 2

Histologically confirmed invasive adenocarcinoma of rectum

Distal border within 8 cm from anal verge

uT2N0, as confirmed by ERUS or endorectal coil MRI

Greatest tumor diameter cannot exceed 4 cm

Excludes:

- **Tumors fixed to adjacent structures on DRE are ineligible**
- **FAP, HNPCC, or inflammatory bowel disease**
- **Prior pelvic radiation**
- **Clinically significant neuropathy**
- **Difficulty or inability to take or absorb oral medications**
- **Other malignancies within the past 5 years (except non melanoma skin cancer or in situ carcinomas.**

Z6041

90 patients accrued (62 in original dose, 28 in revised dose)

All patients that received ≥ 1 treatment cycle and had available AE data were evaluable for AE.

84 patients (57 at original dose and 27 at revised dose) were evaluable for AE.

Demographics

Demographic or Disease Characteristics	Overall n = 84	Original dose n = 57	Revised dose n = 27
Age, years	63 (30-83)	63 (30-80)	64 (45-83)
Gender			
Male	55 (65%)	35 (61%)	20 (74%)
Female	29 (35%)	22 (39%)	7 (26%)
ECOG PS			
0	70 (83%)	49 (86%)	21 (78%)
1	13 (16%)	7 (12%)	6 (22%)
2	1 (1%)	1 (2%)	0 (0%)
Tumor Size, cm	2.9 ± 0.8	2.8 ± 0.8	2.9 ± 0.7
Tumor Location			
Anterior	16 (19%)	11 (19%)	5 (19%)
Posterior	43 (51%)	32 (56%)	11 (41%)
Left Lateral	18 (21%)	11 (19%)	7 (26%)
Right Lateral	7 (8%)	3 (5%)	4 (15%)
Distance from Anal Verge, (distal) cm	5.1 ± 2	4.9 ± 1.9	5.4 ± 2.1

Pathological tumor characteristics

Garcia-Aguilar, et al, ASCO 2010

Pathology	Overall n = 77	Original dose n= 52	Revised dose n = 25
Resected tumor margins free of tumor			
Yes	76 (99%)	52 (100%)	24 (96%)
No	1 (1%)	0 (0%)	1 (4%)
Pathologic tumor size, cm *	0.9 ± 1.1	0.9 ± 1.1	0.9 ± 1
missing	2	2	0
Tumor T stage			
T0	34 (44%)	25 (48%)	9 (36%)
Tis	5 (7%)	3 (6%)	2 (8%)
T1	10 (13%)	7 (13%)	3 (12%)
T2	23 (30%)	14 (27%)	9 (36%)
T3	4 (5%)	2 (4%)	2 (8%)
Tx Ψ	1 (1%)	1 (2%)	0 (0%)
Clinical Complete Response			
Yes	43 (56%)	30 (58%)	13 (52%)
No	34 (44%)	22 (42%)	12 (48%)

* Mean ± standard deviation is shown.

Ψ This patient was not a T0 because the presence of residual cancer cells was reported.

Chemoradiation Grade ≥ 3 AE's

	Original dose N = 57	Revised dose N = 27
≥ G3 AE regardless of attribution	25 (44%)	9 (33%)
Possibly related	25 (44%)	8 (30%)

Most common AEs during CRT

Adverse Event	Overall n = 84		Original dose n = 57		Revised dose n = 27	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Gastrointestinal	18 (21%)	1 (1%)	15 (26%)	1 (2%)	3 (11%)	0 (0%)
Dermatologic	8 (10%)	0 (0%)	6 (11%)	0 (0%)	2 (7%)	0 (0%)
Hematologic	8 (10%)	1 (1%)	3 (5%)	1 (2%)	5 (19%)	0 (0%)
Pain	5 (6%)	1 (1%)	3 (5%)	1 (2%)	2 (7%)	0 (0%)
Metabolic	3 (4%)	2 (2%)	2 (4%)	1 (2%)	1 (4%)	1 (4%)

Ψ Adverse event at least possibly attributed to CRT for CRT visits 3 to 8.
Note: No Grade 5 fatal toxicity was observed.

Most common grade 3 AEs within 60 days of Local Excision

Adverse Event	Overall n = 77	Original dose n= 52	Revised dose n = 25
Rectal Pain	6 (8%)	5 (10%)	1 (4%)
Hemorrhage	2 (3%)	1 (2%)	1 (4%)
Infection	2 (3%)	1 (2%)	1 (4%)
Urinary Retention	2 (3%)	1 (2%)	1 (4%)
Anal Incontinence	1 (1%)	1 (2%)	0 (0%)
Overall Ψ	12 (16%)	7 (13%)	5 (20%)

Ψ Number of patients who experienced any Grade 3 complication.

Chemoradiation

CRT	Overall n = 84	Original dose n = 57	Revised dose n = 27
Capecitabine total dose (mg/m^2) **patients missing**	755 ± 199.6 3	824.9 ± 182 3	615.3 ± 157 0
Oxaliplatin total dose (mg/m^2) **patients missing**	36.1 ± 8.8 1	35.9 ± 7.9 1	36.5 ± 10.7 0
Radiotherapy total dose (Gy)	51.8 ± 5·7	52.2 ± 6·8	51 ± 1.4
Chemotherapy completed per protocol Yes No	 68 (81%) 16 (19%)	 48 (84%) 9 (16%)	 20 (74%) 7 (26%)
Chemotherapy delayed or modified Yes No	 41 (49%) 43 (51%)	 26 (46%) 31 (54%)	 15 (56%) 12 (44%)
Radiotherapy completed per protocol Yes No	 74 (88%) 10 (12%)	 47 (83%) 10 (18%)	 27 (100%) 0 (0%)
Radiotherapy interrupted Yes No	 35 (42%) 49 (58%)	 27 (47%) 30 (53%)	 8 (30%) 19 (70%)

AE profile and pCR

	pCR		
	Yes	No	p-value
Original dose			
n	26	31	
At least one grade 3+ AE			0.1075
Yes (25)	8 (32.0%)	17 (68.0%)	
No (32)	18 (56.3%)	14 (43.7%)	
Revised dose			
n	10	17	
At least one grade 3+ AE			0.4147
Yes (8)	4 (50%)	4 (50%)	
No (19)	6 (31.6%)	13 (68.4%)	

Original Dose: Dose modification and pCR

	PCR		
	Yes (n=26)	No (n=31)	p-value
Was chemo permanently discontinued during the treatment?			0.2748
Yes (9)	6 (66.7%)	3 (33.3%)	
No (48)	20 (41.7%)	28 (58.3%)	
Was radiotherapy completed?			0.0155
Yes (47)	25 (53.2%)	22 (46.8%)	
No (10)	1 (10.0%)	9 (90.0%)	
Was radiotherapy interrupted?			0.5966
Yes (27)	11 (40.7%)	16 (59.3%)	
No (30)	15 (50.0%)	15 (50.0%)	
No (19)	6 (31.6%)	13 (68.4%)	

For the Original Dose group, completing radiotherapy increased the likelihood of having a pCR at LE

Revised Dose: Dose modification and pCR

	PCR		
	Yes (n=10)	No (n=17)	p-value
Was chemo permanently discontinued during the treatment?			0.2040
Yes (7)	1 (14.3%)	6 (85.7%)	
No (20)	9 (45.0%)	11 (55.0%)	
Was radiotherapy completed? (Yes)			-
Yes (27)	10 (100%)	17 (100.0%)	
No (0)	0 (0.0%)	0 (0.0%)	
Was radiotherapy interrupted? (Yes)			0.4147
Yes (8)	4 (50.0%)	4 (50.0%)	
No (19)	6 (31.6%)	13 (68.4%)	

Conclusions

Despite a high pCR rate, chemoradiation with capecitabine and oxaliplatin led to unacceptably high toxicity, even with lowering the dose of capecitabine

Most common ≥ grade 3 AE's were GI, hematologic, dermatologic, pain, and metabolic.

In the original dose group, having at least one ≥ grade 3 AE increased the likelihood of delaying/modifying chemotherapy and increased the likelihood of interrupting radiotherapy

In the original dose group, completing radiotherapy increased the likelihood of having a pCR at LE.

Follow up trial planned.

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ACOSOG Data and Statistical Office

ACOSOG Operations Office

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