N1048

A Phase II/III Trial of Neoadjuvant FOLFOX With Selective Use of Combined Modality Chemoradiation Versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection With Total Mesorectal Excision (PROSPECT)

ClinicalTrials.gov Identifier: NCT01515787

Study Background

Trial Description

The standard treatment for locally advanced rectal cancer involves chemotherapy and radiation, known as 5FUCMT, (the chemotherapy drugs 5-fluorouracil/capecitabine and radiation therapy) prior to surgery. Although radiation therapy to the pelvis has been a standard and important part of treatment for rectal cancer and has been shown to decrease the risk of the cancer coming back in the same area in the pelvis, some patients experience undesirable side effects from the radiation and there have been important advances in chemotherapy, surgery, and radiation which may be of benefit. The purpose of this study is to compare the effects, both good and bad, of the standard treatment of chemotherapy and radiation to chemotherapy using a combination regimen known as FOLFOX, (the drugs 5-fluorouracil (5-FU), oxaliplatin and leucovorin) and selective use of the standard treatment, depending on response to the FOLFOX. The drugs in the FOLFOX regimen are all FDA (Food and Drug Administration) approved and have been used routinely to treat patients with advanced colorectal cancer.

Arms:

Group 1: (Experimental): Patients will receive FOLFOX chemotherapy once every two weeks for 6 cycles total over a period of 12 weeks. After completing FOLFOX chemotherapy, the patient will have an MRI scan or endorectal ultrasound (ERUS) to examine the tumor. If the tumor has not decreased in size by at least 20%, the patient will receive 5FUCMT (radiation with chemotherapy). If the tumor has decreased in size by 20%, then the patient will proceed directly to surgery. If all borders of the tumor are normal post surgery, then the patient receives six additional cycles of FOLFOX chemotherapy. If all borders of the tumor are not normal then the patient receives chemoradiation therapy for 5.5 weeks after surgery. After chemoradiation, additional cycles of FOLFOX or similar chemotherapy

will be recommended for 4 cycles or 8 weeks. Patient observation with follow up evaluations and event monitoring will occur up to 8 years post randomization.

Group 2: (Active Comparator): Patients receive 5FUCMT including chemotherapy and radiation therapy for 5.5 weeks. Patients will be given either 5-fluorouracil or capecitabine and radiation therapy. After the chemoradiation therapy is completed, patients will proceed directly to surgery. Post-surgery, patients will receive FOLFOX chemotherapy once every two weeks for 8 cycles total over a period of 16 weeks. Patient observation with follow up evaluations and event monitoring will occur up to 8 years post randomization.

Objectives:

- OUTLINE:
  This is a multicenter, phase II/III study. Patients are stratified according to ECOG performance status (0 or 1 vs 2) and randomized to 1 of 2 treatment regimens. Patients will receive full supportive care while on this study.
  OBJECTIVES:
  Primary
  1. Phase II component: To assure that neoadjuvant FOLFOX followed by selective use of 5FUCMT group (Group 1) maintains the current high rate of pelvic R0 resection and is consistent with non-inferiority for time to local recurrence (TLR).
  2. Phase III component: To compare neoadjuvant FOLFOX followed by selective use of 5FUCMT (Group 1) to standard 5FUCMT (Group 2) with respect to the primary endpoint of the Disease-Free Survival (DFS).
  Secondary
  1. To determine if the neoadjuvant FOLFOX followed by selective use of 5FUCMT (Group 1) is non-inferior to the standard group 5FUCMT (Group 2) with respect to the proportion of patients who achieve a pathologic complete response (pCR) at the time of surgical resection.
  2. To determine if the neoadjuvant FOLFOX followed by selective use of 5FUCMT (Group 1) is non-inferior to the standard 5FUCMT (Group 2) with respect to overall survival.
  3. To evaluate and compare the adverse event profile and surgery complications between two groups.
  4. To estimate the proportion of patients in the selective group (Group 1) who receive: 1) pre-operative 5FUCMT; 2) post-operative 5FUCMT; 3) either pre- or post-operative 5FUCMT.
  5. To determine if the neoadjuvant FOLFOX followed by selective use of 5FUCMT (Group 1) is non-inferior to the standard 5FUCMT (Group 2) with respect to Local Recurrence (TLR)
  6. To determine if the neoadjuvant FOLFOX followed by selective use of 5FUCMT (Group 1) is non-inferior to the standard 5FUCMT (Group 2) with respect to

Neoadjuvant Response Score (NAR)

Event monitoring of patients will continue up to 8 years post randomization.

Study Milestones:

Start date: June 12, 2012

Primary Completion Date: December 31, 2022

Publication Information:

Analysis Type: Primary

PubMed ID: 37272534

Citation: Schrag D, Shi Q, Weiser MR, Gollub MJ, Saltz LB, Musher BL. New England Journal of Medicine. 2023;389(4):322-334, doi: 10.1056/NEJMoa2303269.

Associated Datasets: NCT01515787-D1-Dataset.csv (final), NCT01515787-D2-Dataset.csv (ae)

Dataset Information:

Dataset Name: NCT01515787-D1-Dataset.csv (final)

Description: Dataset NCT01515787-D1-Dataset.csv (final) is one of 2 datasets associated with PubMed ID 37272534. This dataset contains data presented in the primary manuscript and supplementary tables.

Data can be used to approximate published study findings, but exact reproduction of previous manuscripts may not be possible in some cases (e.g., when data must be modified for de-identification purposes or have undergone further data cleaning).

Blank values indicate data not applicable or missing, except where otherwise noted.

NCT01515787-D1-Dataset.csv (final) Data Dictionary:

LABEL	NAME	ELEMENTS	COMMENTS
Race	racedesc_draft	American Indian or Alaskan Native, Asian, Black or African American, Multiple Races Reported, Native Hawaiian or Pacific Islander, Not reported: patient refused or not available, Unknown: Patient unsure, White	
Clinical T stage at baseline (Baseline Clinical and Radiology Assessment Form)	tgt	T2, T3, TX	
Clinical N stage at baseline (Baseline Clinical and Radiology Assessment Form)	tgn	N0/X, N1, N2	
N stage: Positive/negative	stg_pn	N-, N+	
Consort flow	pt_flow_consort	Decided not to receive intervention,	

LABEL	NAME	ELEMENTS	COMMENTS
		Discontinued therapy: Decided to discontinue therapy, Discontinued therapy: Died, Discontinued therapy: Had adverse events, Discontinued therapy: Had complicating disease, Discontinued therapy: Had other reason, Discontinued therapy: Had tumor progression or more extensive tumor, Discontinued therapy: Opted to watch and wait, Discontinued therapy: Underwent alternative therapy, Discontinued therapy: Was lost to follow-up, Discontinued therapy: Were deemed ineligible, Discontinued therapy: Withdrew, Had disease progression, Were deemed ineligible, Withdrew	
Reason for neoadjuvant chemoradiotherapy in the FOLFOX + selective 5FUCMT arm	chemorad	Did not meet the clinical response threshold of a 20% decrease in primary tumor size, Fewer than 6 cycles of FOLFOX, Treating physician or patient opted for chemoradiotherapy	
Did the patient receive treatment?	treatment	No, Yes	
Pathologic M Stage	PATHSTGM	M0, M1a	
ECOG performance	ps_gc	0 or 1, 2	

LABEL	NAME	ELEMENTS	COMMENTS
status at randomization			
Disease-free Survival (DFS) Status	dfs_status	Censor, Event	
Disease-free Survival (DFS) Days	dfs_days		
Time to Local Recurrence (TLR) Status	tlr_status	Censor, Event	
Time to Local Recurrence (TLR) Days	tlr_days		
What post-operative chemotherapy regimen was started?	CHEM_RX	5FU alone (with or without leucovorin), Capecitabine alone, CAPOX (capecitabine and oxaliplatin), FOLFIRI (5FU and irinotecan), FOLFOX (5FU and oxaliplatin), Other regimen	
How many total cycles of post-operative chemotherapy were actually administered? (cycles)	ADMCYCL	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12	
Did patient receive any post-operative chemotherapy?	POSTCHEM	No, Yes	
Did the patient receive any post-operative adjuvant radiation therapy to the pelvis?	POSTOPRT	No, Yes	
Overall Survival (OS) Status	os_status	Censor, Event	

LABEL	NAME	ELEMENTS	COMMENTS
Overall Survival (Days)	os_days		
Did the patient have a pelvic MRI?	MRI_DONE	No, Yes	
Radial margin category	RMCAT	Negative, but close (>1mm but less than or equal to 3mm), Negative and >3mm, Positive (less than or equal to 1mm is considered positive per AJCC 7th Edition)	
Completeness of rectal resection	COMRESCT	Pelvic R0, R1, R2	
Did the patient meet the criteria for pathologic complete response (pCR)?	PCR	No, Yes	
Time interval of randomization to surgery, weeks	rnd_to_surg		
Time interval of End of total neoadjuvant therapy to surgery, weeks	last_tnt		One patient has a negative value. The patient had surgery 2 days after starting cycle 1 treatment. Resulting in -12 days when adding 14 days per the analysis.
Age (years)	AGE		
Group	ARM	5FUCRT, FOLFOX + selective 5FUCMT	

LABEL	NAME	ELEMENTS	COMMENTS
Country of Residence	COUNTRYNAME	Canada, Switzerland, United States	
Sex	GENDERDESC	Female, Male	
Highest education level	EDUCAT	College graduate or more, High school graduate or GED, Less than high school, Some college	
History of diabetes	DIAB_HX	No, Yes	
History of cardiovascular disease	CVDIS_HX	No, Yes	
Surgeon Assessment of Primary Rectal Tumor	RASSESS	Rectal tumor not palpable, Rectal tumor palpable	
Rectal tumor location (distance from anal verge) (cm)	RDISTAV	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 25	
RT treatment break > 7 days	RT7DAY	No, Unknown, Yes	
ECOG performance status at beginning of first cycle of treatment	ps	0, 1, 2	
5FU relative dose intensity in the FOLFOX + selective 5FUCMT arm	fu_rd_cat	Less than full dose but at least 75% of planned dose of 5FU, With full dose of 5FU	
Oxaliplatin relative dose intensity in the FOLFOX + selective	ox_rd_cat	< 75% of planned dose of Oxaliplatin, Less than full dose but at least 75% of planned dose of Oxaliplatin, With full	

LABEL	NAME	ELEMENTS	COMMENTS
5FUCMT arm		dose of Oxaliplatin	
If patient had MSI testing, MSI testing result	MSIRSLT	MSI-High/dMMR, MSI-Stable/MSI-Low/pMMR	
Continuous Body Mass Index (BMI)	bmi		
Received adequate amount of FOLFOX	folfox_dosage	greater than or equal to 5 cycles of FOLFOX, Received < 3 cycles of FOLFOX, Received 3 to 4 cycles of FOLFOX	
Received total dose of pre-operative Radiation Therapy (RT)	totdose_cat	< 45 Gy, At least 45 Gy, Full dose of 50.4 Gy	
Pathologic T category	PATHSTGT_surgpth	ypT0, ypT1, ypT2, ypT3, ypT4	
Pathologic N category	PATHSTGN_surgpth	ypN0, ypN1, ypN2	
Ethnicity	ethnicity	Hispanic or Latino, Not Hispanic or Latino, Unknown or not reported	
Duration from surgery to initiation of post-operative treatment (chemotherapy or chemoradiation), weeks	surg_to_spostop		
Duration from surgery to last date of post-operative treatment (chemotherapy or chemoradiation), weeks	surg_to_lpostop		
Total treatment duration, from	rnd_to_postop		

LABEL	NAME	ELEMENTS	COMMENTS
randomization to last date of post-operative treatment (chemotherapy or chemoradiation), weeks			
Clinical stage at baseline (Onstudy Form)	STG	cT2N1, cT3N0, cT3N1	
Tumor within 3mm or less of mesorectal fascia	MM3	No, Yes	
pCRs and Tumor regression grading among non pCRs	pcr_TRGRADE	TRG-0 (Complete response; no viable cancer cells), TRG-1 (Moderate response; single cells or small groups of cancer cells), TRG-2 (Minimal response; residual cancer outgrown by fibrosis), TRG-3 (Poor response; minimal or no tumor kill, extensive residual cancer)	
Type of surgery	surg_type	Abdominal Perineal Resection (APR), Non-APR	
Histologic Grade	hist	G1 (Well differentiated or G2 (Moderately differentiated), G3 (Poorly differentiated) or G4 (Undifferentiated, anaplastic), GX (Grade cannot be assessed)	
De-identified ID	deid		
Did Patient have	surg_yn	No, Yes	

LABEL	NAME	ELEMENTS	COMMENTS
Surgery?			