(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 2, Page No: 428-434
March-April 2022

IJMSCR

Role Of Total Neoadjuvant Therapy In Rectal Cancer: Should It Be The Standard Of Care

Shreyasee Karmakar, MD[1], Pranav Chadha,DNB[1]
Department of Radiation Oncology, Kokilaben Dhirubhai Ambani Hospital, Mumbai

***Corresponding Author:**
Shreyasee Karmakar
Department of Radiation Oncology, Kokilaben Dhirubhai Ambani Hospital, Mumbai

Type of Publication: Review article
Conflicts of Interest: Nil

Abstract

Total neoadjuvant therapy (TNT) incorporates both chemotherapy and chemoradiotherapy prior to surgery and its role is currently being explored in rectal cancer. TNT is postulated to offer several advantages like down-staging the primary tumor, reducing occult metastasis, increase compliance to treatment and thereby result in improved surgical and survival outcomes. We explored the available data TNT and its evaluated its current role in management of rectal cancers. We found TNT to be a prudent approach resulting in increased rates of pathological complete response and prolonging disease-free survival. In conclusion, TNT seems to be feasible and safe, however robust data is still awaited.

Keywords: Total neoadjuvant therapy, Rectal Cancer, Radiotherapy, Neoadjuvant chemoradiotherapy, Rectal Cancer Management

Introduction

Colorectal cancer comprises around 10% of overall cancers diagnosed worldwide and is estimated to result in around 935,000 annual deaths [1]. The current management of locally advanced rectal cancer (LARC) is a tri-modality approach comprising of neoadjuvant chemoradiotherapy (NACTRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy [2]. This multimodality approach has significantly improved overall survival and decreased local recurrence by around 20-25% [34]. However, despite advances in all these therapies, a high rate of distant metastases has been reported [5] and this, in turn, results in enhanced mortality. The role of addition of adjuvant chemotherapy is controversial; while few studies have shown no benefit in terms of improved disease-free survival (DFS), overall survival (OS), or decreased recurrences, a meta-analysis has shown improved DFS and lesser recurrences in patients whose primary tumor was 10-15cm from the anal verge [67]. It is also postulated that patients having pathological complete response post-NACTRT may not have additional benefit with adjuvant chemotherapy. Poor compliance to adjuvant chemotherapy due to post-operative complications like leakage, pain, poor general condition, stoma, etc is also a commonly encountered problem [8]. It has been reported that less than 50% of the patients complete adjuvant chemotherapy without delay or interruption. Thus, other modes of delivering chemotherapy were explored.

Total neoadjuvant therapy (TNT) is a strategy that incorporates both chemotherapy and chemoradiotherapy ere surgery. It is assumed that TNT offers several advantages like down-staging the primary tumor, reducing occult metastasis, help assess chemo-sensitivity, and strengthening compliance to treatment. These in turn would produce improved surgical and survival outcomes. TNT is currently endorsed in NCCN guidelines as an alternative method of treatment in LARC, however, the data available is limited and is currently evolving [2]. In this exposition, we aim to explore the current role of TNT and its available data.

Achieving Pathological Complete Response

Pathological complete response (pCR) is the absence of viable malignant cells in the resected sample and is considered as a marker for good prognosis in rectal cancer patients [910]. Several studies have reported that patients of LARC receiving NACTRT have pCR rates up to a tune of 10-30% [11912]. It is seen that pCR rates affect survival outcomes. In the NACTRT arm of the German rectal trial (CAO/ARO/AIO-94 trial), 5-year DFS was 86% in patients who had achieved pCR vs 63% in those who had an incomplete response [13]. Another study by *Maas et al* showed 83.3% 5year DFS in patients with pCR vs 65.6% for those without pCR; 5-year metastasis-free survival was 88.8% vs 74.9% and 5yr OS was 87.6% vs 76.4% in patients with and without pCR respectively [14].

Calvo et al in 2006 compared pCR outcomes in LARC patients receiving NACTRT with or without induction oxaliplatin and found significantly improved pCR in patients receiving induction chemotherapy (p= 0.006) [15]. Another multicentric, phase II trial evaluated patients receiving NACTRT followed by pre-operative oxaliplatin either 2, 4, or 6 cycles. They found improved pCR rates with 6 cycles of preoperative chemotherapy with decreased surgical technical difficulties and postoperative complications [16]. A retrospective cohort analysis from Memorial Sloan Kettering Cancer Centre evaluated TNT with standard treatment in 628 patients. Of these, 296/320 patients of the standard treatment group and 235/308 patients of TNT group subsequently underwent surgery. In patients undergoing surgery, pCR was comparable in both groups while among patients who were observed, sustained complete clinical response with non-operative treatment was seen in 92% in TNT group vs 79% in the standard treatment group at 12 months [17]. These findings were corroborated by few other studies [18192021]. A systematic review and meta-analysis found a pooled prevalence of pCR to be 29.9% with TNT and 14.9% with standard treatment [22]. A recent study also showed improved pCR rates with TNT, though not statistically significant (pCR 16.9% with TNT vs 13.1% with NACTRT, p=0.12) [23]. In the RAPIDO trial comparing standard treatment with short-course radiotherapy followed by preoperative chemotherapy, increased pCR was observed with pre-operative chemotherapy (28% vs 14%) [21].

Surgical Outcomes

Data regarding surgical outcomes like sphincter-sparing surgery and ileostomy requirements following TNT is sparse. *Calvo et al* reported sphincter preservation surgery in 68% of patients receiving 4 cycles neoadjuvant oxaliplatin with NACTRT in contrast to 61% of patients who received NACTRT alone [15]. *Markovina et al* studied patients treated with TNT in two institutions and compared outcomes with historical cohorts. They found no difference in sphincter preservation surgeries between TNT and control groups, however, the rates of R1 and R2 resection were higher in the control group [19]. Similar outcomes were seen in few other studies [1618]. The rates of diverting ileostomy were found to be comparable in the two studies. Even in the meta-analysis by *Kasi et al*, no difference in sphincter sparing surgery and ileostomy requirements were observed between the two treatment modalities [22].

Survival Outcomes

TNT is found to be associated with improved survival outcomes. *Markovina et al* reported significantly better 3 year DFS with TNT (85% vs 68%, p=0.03) , however, this did not translate into an overall survival benefit [19]. A similar finding was observed by Conroy et al in their phase III multicentre randomized trial (3-year DFS 68.5% vs 75.7% in TNT vs without TNT) (22). Other studies also reported improved DFS with TNT [16,22].

Compliance, Toxicity, Post-Operative Complications:

Toxicities and compliance of patients to therapy are of utmost importance given the intensive neoadjuvant therapy. In the study by *Calvo et al*, grade 3 gastrointestinal toxicity was seen in only 6% of patients and no grade 3 neurotoxicity was reported [15]. Two other studies reported grade 3-4 hematological toxicities and one study reported grade 5 late toxicity in 2 patients resulting in post-surgical peritonitis and necrotic ostomy [1619]. Higher toxicity was also observed with TNT in the RAPIDO trial. *Conroy et al* reported neutropenia and diarrhea as the most common grade 3-4 toxicities associated with neoadjuvant chemotherapy [20]. They also observed

Volume 5, Issue 2; March-April 2022; Page No 428-434

decreased neurotoxicity with preoperative chemotherapy and considered it to be a more prudent approach compared to adjuvant chemotherapy.

Sequencing Of TNT

TNT can be delivered by 2 strategies - either administering neoadjuvant chemotherapy between CTRT and surgery, or delivering neoadjuvant chemotherapy followed by CTRT followed by surgery. Both approaches have been evaluated by various studies. The recent phase II OPRA study randomized patients to two neoadjuvant treatment arms: either induction chemotherapy (8 cycles of FOLFOX [or equivalent CAPOX]) followed by CTRT, or CTRT followed by 8 cycles of FOLFOX. After 8-12 weeks of completion of therapy, patients were re-evaluated and those having complete or near-complete response were offered wait and watch policy. Patients with incomplete response had to undergo TME. At a median follow-up of 2.1years, it was seen that upfront CTRT followed by consolidative chemotherapy resulted in better wait and watch strategy rates. Few studies with their sequencing and outcomes are given in table 1.

Table 1: Various TNT studies and outcomes

Study	No. of patients	STUDY DESIGN	REGIMEN	pCR		Sphincter preservation		Post-operative complications		Survival outcomes
				TNT	NCRT	TNT	NCRT	TNT	NCRT	
Calvo et al (2006) [15]	52	Prospective	NCRT vs FOLFOX (4 cycles) --> CTRT	29%	8%	68%	61%	31%	36%	NA
CONTRE (2017)[24]	39	Prospective, single arm	mFOLFOX6 (8cycles) --> NCRT	33%	-	-	-	6%	-	NA
Dueland (2016) [25]	97	Phase 2, single arm	2cycles FLOX --> CTRT	17%	-	-	-	NA	-	5yr DFS 61%, 5yr OS-83%
Schou (2012) [26]	84	Prospective, single arm	2cycles CAPOX --> NCRT	23%	-	-	-	9%	-	5yr DFS 63%, 5yr OS-67%
Garcia-aguilar et al (2015) [16]	259	Phase 2, non-randomised four arm, multicentric	NCRT vs NCRT --> 2 cycles mFOLFOX6	25%	18%	75%	77% (p-value 0.68)	6%	15%	NA
			NCRT vs NCRT -->4 cycles mFOLFOX6	30%		75%		4%		

Volume 5, Issue 2; March-April 2022; Page No 428-434

			NCRT vs NCRT --> 6 cycles mFOLFOX6	38%		68%		9%		
Bujko (Polish II trial) (2016) [27]	515	Phase 3, randomized	RT --> 3 cycles FOLFOX4	16%				29%		3yr DFS 53%, 3yr OS-73%

Abbreviations: NCRT- Neoadjuvant chemoradiotherapy, TNT- Total neoadjuvant therapy arm, NA- Not available, FOLFOX6- 5-fluorouracil, leucovorin and oxaliplatin, mFOLFOX6- modified FOLFOX6, FLOX- 5-fluorouracil + Folinic acid + Oxaliplatin, CAPOX- Capecitabine + Oxaliplatin, DFS- Disease-free survival, OS- Overall survival.

Role In Recurrent Setting

To our knowledge, the role of TNT in locally recurrent rectal cancer has been reported by only one study. *Van Zoggel et al* compared patients receiving TNT with those receiving NACTRT at the same time interval [18]. TNT included 3-4 cycles of oxaliplatin and 5-fluorouracil based chemotherapy followed by chemoradiotherapy (30Gy radiation with concomitant oral capecitabine). Of 58 patients receiving TNT, they found no difference in R0 resection but a significant increase in pCR rates (17% with TNT vs 4% without TNT, p=0.015) as compared to those not receiving TNT.

Predictive And Prognostic Markers For TNT

The role of predictive biomarkers and molecular profiling of tumors is currently emerging. The NCCN guidelines currently recommend microsatellite instability (MSI) or mismatch repair testing in patients with colorectal cancer [2]. Around 15% of patients with colorectal cancer have MSI and MSI as a predictor of response to NACTRT has been investigated. Identifying a cohort of a patient based on MSI who may achieve pCR with TNT may help to improve outcomes. *Hasan et al* studied around 5000 patients of LARC from National Cancer Database (NCDB) and investigated the association between MSI and pCR [28]. They found MSI to be an independent predictor of pCR, with MSI + patients having significantly reduced pCR and 5year survival of patients with pCR being 93%. However, a recently published meta-analysis evaluated around 5800 patients and found no significant association between MSI and pCR (p=0.35) [29]. Given the contradicting results of the studies, the role of incorporating MSI as a factor for selecting patients for TNT needs to be further evaluated.

Various surrogates like downsizing of tumor, down-staging, and tumor regression grade (TRG) serve as an indirect measure to assess tumor response. The Neoadjuvant rectal score (NAR) is a short-term surrogate endpoint which was proposed by National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group (NRG) Oncology groups and was developed based on Valentini's nomogram for OS, but included only clinical T stage and pathological T and N stage [30]. The randomized phase III CAO/ARO/AIO-04 trial found the NAR score as an independent prognostic factor for DFS, thus validating it further [31]. However, this was contradicted by a study from Netherlands Cancer Registry evaluating around 6500 patients who did not find NAR as a surrogate for survival [32].

Role Of Targetted Therapy In TNT

Few recent studies are exploring the benefit of administering novel radiation sensitizers and immunotherapeutic agents in TNT, however mature data is awaited. The VOLTAGE-A study evaluated the role of pre-operative nivolumab following NACTRT. They reported a pCR rate of 30% in microsatellite stable (MSS) patients and 60% in patients with micro-instability high (MSI-H) with acceptable toxicities [33]. The benefit of adding the anti-angiogenic drug aflibercept before NACTRT has been explored by randomized, phase II GEMCAD 1402 trial; the preliminary results, though, did not show any improved DFS [34]. Several other studies are evaluating the role of other agents like durvalumab,

Volume 5, Issue 2; March-April 2022; Page No 428-434

avelumab, peposertib, veliparib, etc as a part of TNT, and results are currently awaited [35363738].

Conclusion

Total neoadjuvant chemotherapy seems to be a prudent approach in the treatment of locally advanced rectal cancer given the good oncological outcomes and acceptable toxicities. TNT has been found to result in increased rates of pCR which translates into DFS benefit. However, the benefit of TNT remains to be explored further in large randomized trials. The incorporation of targeted agents in TNT appears to be promising and results of ongoing studies are awaited.

References:

1. Global Cancer Observatory. GLOBOCAN. Published 2020. https://gco.iarc.fr/
2. Benson AB, Venook AP, Al-Hawary MM, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(3):329-359. doi:10.6004/jnccn.2021.0012
3. Havenga K, Enker WE, Norstein J, et al. Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 1999;25(4):368-374. doi:10.1053/ejso.1999.0659
4. Gérard J-P, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24(28):4620-4625. doi:10.1200/JCO.2006.06.7629
5. Bosset J-F, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol. 2014;15(2):184-190. doi:10.1016/S1470-2045(13)70599-0
6. Breugom AJ, Swets M, Bosset J-F, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol. 2015;16(2):200-207. doi:10.1016/S1470-2045(14)71199-4
7. Bujko K, Glimelius B, Valentini V, Michalski W, Spalek M. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: A meta-analysis of randomized trials comparing surgery ± a fluoropyrimidine and surgery + a fluoropyrimidine ± oxaliplatin. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2015;41(6):713-723. doi:10.1016/j.ejso.2015.03.233
8. Khrizman P, Niland JC, Ter Veer A, et al. Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with neoadjuvant therapy: A National Comprehensive Cancer Network analysis. J Clin Oncol. 2013;31(1):30-38. doi:10.1200/JCO.2011.40.3188
9. Park IJ, You YN, Agarwal A, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(15):1770-1776. doi:10.1200/JCO.2011.39.7901
10. Omejc M, Potisek M. Prognostic Significance of Tumor Regression in Locally Advanced Rectal Cancer after Preoperative Radiochemotherapy. Radiol Oncol. 2018;52(1):30-35. doi:10.1515/raon-2017-0059
11. Cotte E, Passot G, Decullier E, et al. Pathologic Response, When Increased by Longer Interval, Is a Marker but Not the Cause of Good Prognosis in Rectal Cancer: 17-year Follow-up of the Lyon R90-01 Randomized Trial. Int J Radiat Oncol Biol Phys. 2016;94(3):544-553. doi:10.1016/j.ijrobp.2015.10.061
12. Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med. 1985;312(23):1465-1472. doi:10.1056/NEJM198506063122301
13. Rödel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(34):8688-8696. doi:10.1200/JCO.2005.02.1329

Volume 5, Issue 2; March-April 2022; Page No 428-434

14. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010;11(9):835-844. doi:10.1016/S1470-2045(10)70172-8
15. Calvo FA, Serrano FJ, Diaz-González JA, et al. Improved incidence of pT0 downstaged surgical specimens in locally advanced rectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and preoperative chemoradiation. Ann Oncol. 2006;17(7):1103-1110. doi:10.1093/annonc/mdl085
16. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015;16(8):957-966. doi:10.1016/S1470-2045(15)00004-2
17. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer. JAMA Oncol. 2018;4(6):e180071. doi:10.1001/jamaoncol.2018.0071
18. van Zoggel DMGI, Bosman SJ, Kusters M, et al. Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer. Br J Surg. 2018;105(4):447-452. doi:10.1002/bjs.10694
19. Markovina S, Youssef F, Roy A, et al. Improved Metastasis- and Disease-Free Survival With Preoperative Sequential Short-Course Radiation Therapy and FOLFOX Chemotherapy for Rectal Cancer Compared With Neoadjuvant Long-Course Chemoradiotherapy: Results of a Matched Pair Analysis. Int J Radiat Oncol Biol Phys. 2017;99(2):417-426. doi:10.1016/j.ijrobp.2017.05.048
20. Conroy T, Bosset J-F, Etienne P-L, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(5):702-715. doi:10.1016/S1470-2045(21)00079-6
21. van der Valk MJM, Marijnen CAM, van Etten B, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2020;147:75-83. doi:10.1016/j.radonc.2020.03.011
22. Kasi A, Abbasi S, Handa S, et al. Total Neoadjuvant Therapy vs Standard Therapy in Locally Advanced Rectal Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(12):1-11. doi:10.1001/jamanetworkopen.2020.30097
23. Zhu J, Liu A, Sun X, et al. Multicenter, Randomized, Phase III Trial of Neoadjuvant Chemoradiation With Capecitabine and Irinotecan Guided by UGT1A1 Status in Patients With Locally Advanced Rectal Cancer. J Clin Oncol. 2020;38(36):4231-4239. doi:10.1200/JCO.20.01932
24. Perez K, Safran H, Sikov W, Vrees M, Klipfel A, Shah N, Schechter S, Oldenburg N, Pricolo V, Rosati K DT. No Title Complete Neoadjuvant Treatment for Rectal Cancer: The Brown University Oncology Group CONTRE Study. Am J Clin Oncol. 40(3):283-287. doi:10.1097/COC.0000000000000149
25. Dueland S, Ree AH, Grøholt KK et al. Oxaliplatin-containing Preoperative Therapy in Locally Advanced Rectal Cancer: Local Response, Toxicity and Long-term Outcome. Clin Oncol (R Coll Radiol). 2016;28(8):532-539. doi:10.1016/j.clon.2016.01.014
26. Schou JV, Larsen FO, Rasch L et al. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. Ann Oncol. 2012;23:2627-2633.
27. Bujko K, Wyrwicz L, Rutkowski A et al. Long-course oxaliplatinbased preoperative chemoradiation versus 5 3 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol. 2016;27:834-842.

Volume 5, Issue 2; March-April 2022; Page No 428-434

28. Hasan S, Renz P, Wegner RE, et al. Microsatellite Instability (MSI) as an Independent Predictor of Pathologic Complete Response (PCR) in Locally Advanced Rectal Cancer: A National Cancer Database (NCDB) Analysis. Ann Surg. 2020;271(4):716-723. doi:10.1097/SLA.0000000000003051
29. O'Connell E, Reynolds IS, McNamara DA, Prehn JHM, Burke JP. Microsatellite instability and response to neoadjuvant chemoradiotherapy in rectal cancer: A systematic review and meta-analysis. Surg Oncol. 2020;34:57-62. doi:10.1016/j.suronc.2020.03.009
30. Valentini V, van Stiphout RGPM, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol Off J Am Soc Clin Oncol. 2011;29(23):3163-3172. doi:10.1200/JCO.2010.33.1595
31. Fokas E, Fietkau R, Hartmann A, et al. Neoadjuvant rectal score as individual-level surrogate for disease-free survival in rectal cancer in the CAO/ARO/AIO-04 randomized phase III trial. Ann Oncol Off J Eur Soc Med Oncol. 2018;29(7):1521-1527. doi:10.1093/annonc/mdy143
32. van der Valk MJM, Vuijk FA, Putter H, van de Velde CJH, Beets GL, Hilling DE. Disqualification of Neoadjuvant Rectal Score Based on Data of 6596 Patients From the Netherlands Cancer Registry. Clin Colorectal Cancer. 2019;18(2):e231-e236. doi:10.1016/j.clcc.2019.01.001
33. Yuki S, Bando H, Tsukada Y, et al. Short-term results of VOLTAGE-A: Nivolumab monotherapy and subsequent radical surgery following preoperative chemoradiotherapy in patients with microsatellite stable and microsatellite instability-high locally advanced rectal cancer. J Clin Oncol. 2020;38(15_suppl):4100. doi:10.1200/JCO.2020.38.15_suppl.4100
34. Fernandez-Martos C, Machado I, Pericay C, et al. Randomized phase II trial of modified (m) FOLFOX6 induction chemotherapy with or without aflibercept before standard chemoradiotherapy (CRT) and total mesorectal excision (TME) in patients with high-risk rectal adenocarcinoma (HRRC): Final results of the . J Clin Oncol. 2020;38(15_suppl):4102. doi:10.1200/JCO.2020.38.15_suppl.4102
35. Capdevila J, Macias Declara I, Riesco Martinez MC, et al. Phase II study of durvalumab plus total neoadjuvant therapy (TNT) in locally advanced rectal cancer: The GEMCAD-1703 DUREC trial. J Clin Oncol. 2020;38(15_suppl):TPS4122-TPS4122. doi:10.1200/JCO.2020.38.15_suppl.TPS4122
36. Romesser PB, Holliday EB, Philip T, et al. A multicenter phase Ib/II study of DNA-PK inhibitor peposertib (M3814) in combination with capecitabine and radiotherapy in patients with locally advanced rectal cancer. J Clin Oncol. 2021;39(3_suppl):TPS144-TPS144. doi:10.1200/JCO.2021.39.3_suppl.TPS144
37. Shamseddine A, Zeidan YH, Kreidieh M, et al. Short-course radiation followed by mFOLFOX-6 plus avelumab for locally-advanced rectal adenocarcinoma. BMC Cancer. 2020;20(1):1-11. doi:10.1186/s12885-020-07333-y
38. Rahma OE, Yothers G, Hong TS, et al. NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally advanced rectal cancer (LARC)—Pembrolizumab experimental arm (EA) primary results. J Clin Oncol. 2021;39(3_suppl):8. doi:10.1200/JCO.2021.39.3_suppl.8

Volume 5, Issue 2; March-April 2022; Page No 428-434