

STUDY PROTOCOL

Open Access



The efficacy and safety of short-course radiotherapy followed by sequential chemotherapy and Cadonilimab for locally advanced rectal cancer: a protocol of a phase II study

Tongzhen Xu^{1†}, Lingling Feng^{2†}, Wenjue Zhang², Haoyue Li¹, Huiying Ma¹, Muyasha Abulimiti², Yutong Tan², Feiyan Deng², Wenting Huang^{3,4}, Shuangmei Zou⁴, Wenyan Kang⁵, Liming Jiang⁶, Ying Wang⁷, Chen Hu⁸, Yinggang Chen^{9*}, Haitao Zhou^{10*}, Yuan Tang^{1*} and Jing Jin^{1,2*}

Abstract

Background For patients with locally advanced rectal cancer (LARC), total neoadjuvant therapy (TNT), namely, intensifying preoperative treatment through the integration of radiotherapy and systemic chemotherapy before surgery, was commonly recommended as the standard treatment. However, the risk of distant metastasis at 3 years remained higher than 20%, and the complete response (CR) rate was less than 30%. Several clinical trials had suggested a higher complete response rate when combining single-agent immunotherapy with short-course radiotherapy (SCRT). The CheckMate 142 study had shown encouraging outcomes of dual immunotherapy and seemingly comparable toxicity for CRC compared with single-agent immunotherapy in historical results. Therefore, dual immunotherapy might be more feasible in conjunction with the TNT paradigm of SCRT. We performed a phase II study to investigate whether the addition of a dual immune checkpoint inhibitor bispecific antibody, Cadonilimab, to SCRT combined with chemotherapy might further increase the clinical benefit and prognosis for LARC patients.

Methods This single-arm, multicenter, prospective, phase II study included patients with pathologically confirmed cT3-T4N0 or cT2-4N + rectal adenocarcinoma with an ECOG performance score of 0 or 1. Bispecific antibody immunotherapy was added to SCRT combined with chemotherapy. Patients enrolled would be treated with SCRT (25 Gy in five fractions over 1 week) for the pelvic cavity, followed by 4 cycles of CAPOX or 6 cycles of mFOLFOX and Cadonilimab. The primary endpoint was the CR rate, which was the ratio of the pathological CR rate plus the clinical CR rate.

[†]Tongzhen Xu and Lingling Feng contributed equally to this work.

*Correspondence:

Yinggang Chen
chygang777@163.com
Haitao Zhou
zhouhaitao01745@163.com
Yuan Tang
tangyuan@cicams.ac.cn
Jing Jin
jinjing@cscso.org.cn

Full list of author information is available at the end of the article



The secondary endpoints included local–regional control, distant metastasis, disease-free survival, overall survival, toxicity profile, quality of life and functional outcome of the rectum. To detect an increase in the complete remission rate from 21.8% to 40% with 80% power, 50 patients were needed.

Discussion This study would provide evidence on the efficacy and safety of SCRT plus bispecific antibody immunotherapy combined with chemotherapy as neoadjuvant therapy for patients with LARC, which might be used as a candidate potential therapy in the future.

Trial registration This phase II trial was prospectively registered at ClinicalTrials.gov, under the identifier NCT05794750.

Keywords Locally advanced rectal cancer, Bispecific antibody immunotherapy, Short-course radiotherapy, Total neoadjuvant therapy, Complete response

Introduction

For patients with locally advanced rectal cancer (LARC), preoperative long-course radiotherapy or chemoradiotherapy (CRT) combined with total mesorectal excision (TME) had been considered as the standard treatment, which greatly decreased local recurrence and improves the tumor resection rate [1, 2]. Short-course radiotherapy (SCRT) with preoperative chemotherapy followed by surgery was also deemed as an efficacious alternative to CRT for LARC. Even though the local recurrence rate had plummeted to less than 10% in the era of gradually increasing adoption of neoadjuvant chemoradiotherapy plus TME surgery for LARC, a considerable proportion of patients with nonmetastatic rectal cancer, especially those with high-risk features, were still at high risk of suffering from distant metastasis with an incidence ranging from 26 to 36% [3–5].

Total neoadjuvant therapy (TNT), standing out as a promising approach, aimed to improve overall survival (OS) by intensifying preoperative treatment to eliminate early micrometastatic lesions through the integration of radiotherapy and systemic chemotherapy before surgery. Randomized studies on TNT for LARC had demonstrated improved rates of distant metastasis-free survival (DMFS) and increased tumor complete response (CR) rates [6]. A better pathological CR (pCR) rate (28% vs 14%, $P < 0.0001$) and improved DMFS [7] were observed in another phase III trial (RAPIDO) for LARC patients treated with SCRT and preoperative chemotherapy. Furthermore, the STELLAR study showed that a TNT paradigm of SCRT followed by neoadjuvant chemotherapy could achieve CR rates (21.8% vs 12.3%, $P = 0.002$) superior to long-course CRT, without compromising on 3-year disease-free survival (DFS) [8]. At present, most studies had shown that the treatment strategy of TNT rather than conventional CRT could achieve better tumor control and a higher CR rate for LARC, especially for those with high-risk features, resulting in increasing possibilities of rectal organ preservation and satisfying quality of life. However, the risk of distant metastasis at

3 years remained higher than 20%, and the CR rate was less than 30% [7, 8].

How to maintain a high CR rate while reducing the distant metastasis rate was challenging and had fallen under spotlight for years. Accumulating evidences had suggested that radiotherapy might also eliminate tumors by activating local and/or systemic immune responses, especially when it was combined with immunotherapy such as immune checkpoint inhibitors [9]. There was a synergistic sensitizing effect when radiotherapy was combined with immune checkpoint inhibitors. Radiotherapy would promote the release of tumor-specific antigens and upregulate the expression of major histocompatibility complex (MHC) on cancer cells to promote tumor antigen presentation to cytotoxic T cells, and it would be easier for immunotherapy drugs to recognize these antigens and facilitate antigen-presenting cells to phagocytize damaged tumor cells [10]. In addition, radiotherapy could result in the reshaping of the tumor microenvironment, reduce immunosuppressive factors and increase the infiltration of effector T cells [11]. Immunotherapy might improve radiosensitivity by normalizing tumor vascularity and hypoxia [12]. There was still a large space worthy of further exploration for the treatment of combining radiotherapy and immunotherapy.

For radiotherapy, most LARC clinical trials were designed to explore the efficacy of combining preoperative long-course CRT with single agent immunotherapy in the TNT setting, some of which had released their final results of pCR rates of 24–32.7% [13–15]. Instead of long-course CRT, SCRT combined with immunotherapy might further improve the pCR rate, because substantial immune-stimulatory potential had been observed in rectal cancer treated with SCRT [16]. The Averectal trial showed that SCRT followed by mFOLOFX6 and Avelumab had an acceptable toxicity profile and a 37.5% pCR rate for LARC, which was better than standard neoadjuvant treatment [17]. Another phase II trial (NCT04231552) also reported a pCR rate of 100% in rectal cancer patients with deficient mismatch repair/

microsatellite instability-high (dMMR/MSI-H) and 46% in patients without mismatch repair defects [18].

For immunotherapy, several clinical studies had demonstrated that combination therapy of anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies and anti-programmed cell death protein-1 (PD-1) antibodies could significantly improve oncological outcomes for some hard-to-treat cancer types. In the first-line treatment of metastatic colorectal cancer (CRC) patients, the dual immunotherapy combination regimen from the CheckMate 142 study and MEDITREME trial had shown high objective response rates (ORR) of 69% and 64.5%, with encouraging progression-free survival and OS at 24 months (74% and 79%, 6.7% and 57.6%, respectively) [19, 20]. In the background of preoperative treatment, the NICHE trial had also indicated that neoadjuvant dual immunotherapy could improve pathological response outcome for early-stage CRC with a pCR rate of 60% in dMMR tumors [21]. However, severe toxicities hampered the further application of dual immunotherapy [19–22].

Cadonilimab, as an immunotherapy agent, was the first anti-PD-1/CTLA-4 bispecific antibody approved in China for relapsed or metastatic cervical cancer [23]. A phase Ia/Ib study on relapsed mesothelioma showed tolerability and encouraging antitumor activity of Cadonilimab [24]. Several phase Ib/II studies on advanced solid tumors, including cervical cancer, esophageal squamous cell carcinoma and hepatocellular carcinoma, had also demonstrated the efficacy and safety of this novel bispecific antibody [25–30]. Anti-PD-1/CTLA-4 bispecific antibody might be more feasible in conjunction with SCRT for LARC. We hypothesized that the addition of a dual immune checkpoint inhibitor bispecific antibody, Cadonilimab, to SCRT combined with chemotherapy might further increase the clinical benefit and prognosis for LARC patients.

Methods/design

Trial design

This was a phase II, multicenter, single-arm, open-label, prospective study (ClinicalTrials.gov Identifier: NCT05794750) for cT3-T4N0 or cT2-4N+ rectal cancer. Bispecific antibody immunotherapy was added to SCRT combined with chemotherapy. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The current protocol was version 2.0 dated October 8, 2022. The protocol and its amendments had been approved by the ethics committee of the Cancer Hospital & Shenzhen Hospital Chinese Academy of Medical Sciences (YW2022-21-3) and the Cancer Hospital Chinese Academy of Medical Sciences (23/283-4025). The bispecific antibody, Cadonilimab, was supported by Akesobio. Response Evaluation Criteria in Solid Tumors

(RECIST) Version 1.1, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 and Eastern Cooperative Oncology Group (ECOG) were adopted to evaluate the tumor response, adverse events (AEs) and performance status, respectively [31–33]. The study design was summarized in Fig. 1.

Eligibility criteria

The inclusion and exclusion criteria for patients were listed in Supplementary Table 1.

Objectives

Primary endpoint

- Percent of patients achieving CR, which was the ratio of pCR rate plus clinical complete response (cCR) rate. A pCR was defined as the absence of tumor cells at the primary site and regional lymph nodes. For the precise judgement and diagnosis of cCR, the cCR criteria set by Mass in 2011 were applied [34] and were shown in Table 1.

Secondary endpoints

- 3-year local–regional recurrence-free survival (LRFS) rate (LRFS was defined as the time from the date of radiation to the first recurrence or progression of tumor within its original site or surrounding region)
- 3-year DMFS rate (DMFS was defined as the time from the date of radiation to the first occurrence of distant metastasis)
- 3-year DFS rate (DFS was defined as the time from the date of radiation to the first occurrence of local–regional failure, distant metastasis, second primary tumor, or death from any cause)
- 3-year OS rate (OS was defined as the time from the date of radiation to death from any cause)
- Toxicity profile (NCI-CTCAE v5.0)
- Assessment of quality of life (QoL) and functional outcome of the rectum

Exploratory endpoints

- The correlation between the expression of immune markers and the distribution of immune cells in tumor tissue or blood and the clinical outcome. These included the application of single-cell transcriptomics and spatial transcriptomics to identify the characteristics of immune cells within the

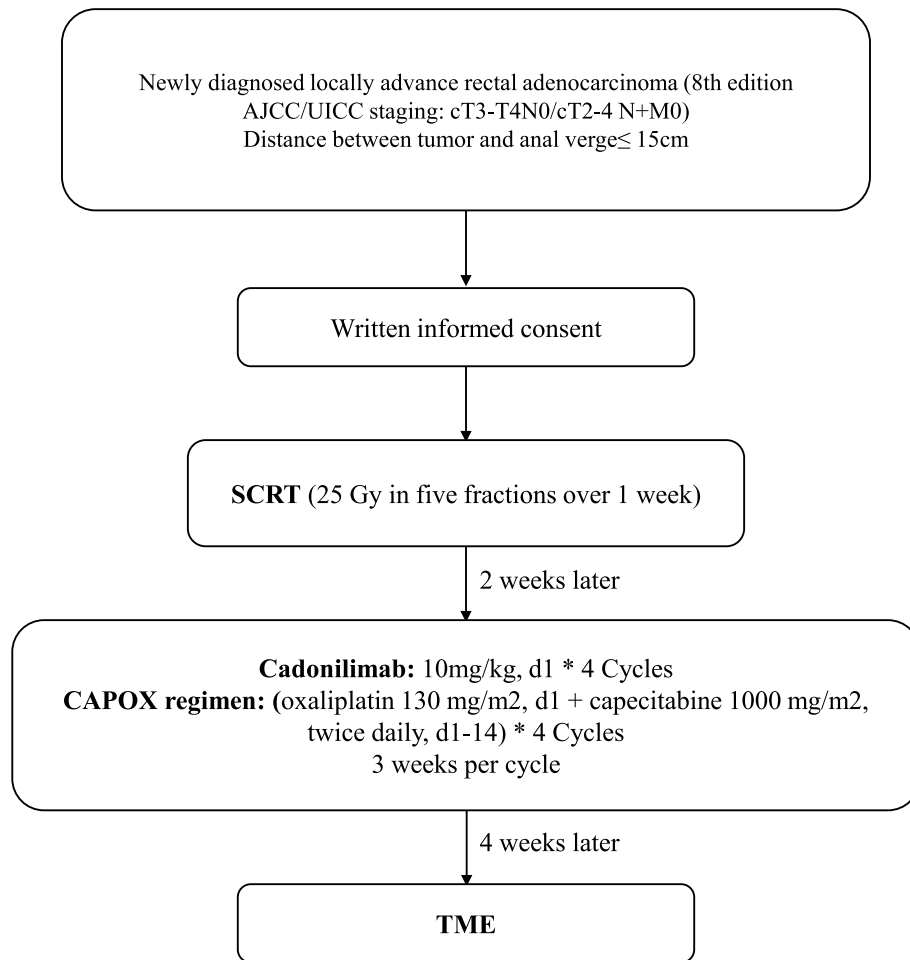


Fig. 1 Study design. Abbreviation: AJCC. American Joint Committee on Cancer; UICC. Union for International Cancer Control; SCRT. Short-course radiotherapy; TME. Total mesorectal excision; Note: The mFOLFOX regimen is an alternative for those who are intolerable with CAPOX regimen. mFOLFOX regimen: (oxaliplatin 85 mg/m2 d1, leucovorin 400 mg/m2 d1 + fluorouracil 400 mg/m2 d1 followed by fluorouracil 2400 mg/m2 as a 44 to 46 hours infusion) * 6 Cycles, 2 weeks per cycle

Table 1 Criteria for clinical complete response

Diagnosis criteria

1. Substantial downsizing with no residual tumor or residual fibrosis only (with low signal on high b-value DWI, if available)
2. No suspicious lymph nodes on MRI
3. No residual tumor at endoscopy or only a small residual erythematous ulcer or scar
4. Negative biopsies from the scar, ulcer, or former tumor location
5. No palpable tumor, when initially palpable with digital rectal examination

Abbreviation: DWI Diffusion weighted imaging, MRI Magnetic resonance imaging

If patients did not meet all of these criteria, the diagnosis of clinical complete response could not be validated

tumor microenvironment, the utilization of Proximity Extension Assay by Olink Proteomics to explore multiple cytokine changes at the protein level and the investigation of the dynamic altera-

tion of peripheral blood mononuclear cells using Cytometry by Time-of-Flight technology.

- The relationship between circulating tumor DNA and the outcome of patients.

Intervention

Neoadjuvant treatment modality

Patients enrolled would be treated with SCRT (25 Gy in five fractions over 1 week) for the pelvic cavity, followed by 4 cycles of CAPOX or 6 cycles of mFOLFOX and Cadonilimab. The CAPOX regimen included oxaliplatin 130 mg/m² d1, and capecitabine 1000 mg/m² bid, d1-14 (3 weeks per cycle). The mFOLFOX regimen was an alternative for those who could not tolerate with CAPOX regimen. It included oxaliplatin 85 mg/m² d1, leucovorin 400 mg/m² d1 plus fluorouracil 400 mg/m² d1 followed by fluorouracil 2400 mg/m² as a 44 to 46 h infusion, repeated every 2 weeks. Cadonilimab (10 mg/kg d1) was administered for 4 cycles (3 weeks per cycle). All patients received intensity-modulated radiation therapy (IMRT), volume modulated arc therapy (VMAT) or tomotherapy (TOMO). Before rectal cancer radiotherapy, patients underwent preparatory measures for accurate positioning. These included emptying the rectum as much as possible, with the option of using stool softeners like liquid paraffin if necessary. One hour before positioning, patients voided their bladder and drink 1000ml of water without voiding again to ensure bladder filling. Lead markers were also positioned at the anal verge to aid localization during treatment. CT-based planning was conducted with axial images taken at intervals of 5 mm, covering the upper lumbar spine to the mid-femur and MR scan was also collected on the same positioning condition for fusion with the planning CT-scan. Intravenous contrast was required to enhance the visualization of the iliac and inguinal vessels. The clinical target volume (CTV) included the primary tumor, regional lymph nodes, and pelvic regions at risk according to our previous STELLAR study. The mesorectum, presacral space, internal iliac nodes, obturator nodes, and ischio-rectal fossa were covered within the CTV, and if the rectal tumor was staged as T4b, external iliac nodes should be included. The superior border was defined as the sacral promontory. The inferior border was 2–3 cm distal to the lower pole of the tumor. Expansion of the CTV to the planning target volume (PTV) was 0.5–1.0 cm.

During treatment, Cadonilimab dose adjustment was not allowed, but delayed doses were permitted for up to 12 weeks. Immune-related adverse events (irAEs) were defined as adverse events related to immune checkpoint inhibitors, consistent with immune-mediated mechanisms and unable to be attributed to other certain causes. Criteria for Cadonilimab pausing and discontinuing when specific irAEs appeared in the neoadjuvant treatment were shown in Supplementary Table 2. For irAEs unmentioned above or some special toxicities, the practice guidelines of the management of immune-related adverse events in patients treated with immune

checkpoint inhibitors would be referenced [35]. For investigator-assessed grade 3 or higher non-irAEs associated with Cadonilimab, the administration of Cadonilimab could be withheld for clinical management, and the decision to continue medication could be made at the discretion of the investigator until the adverse events had resolved or improved. Dose interruptions were unnecessary for AEs that were clearly unrelated to cadonilimab or for laboratory abnormalities that were not clinically significant. All toxicities were graded according to NCI-CTCAE v5.0.

Criteria for dose adjustment of neoadjuvant chemotherapy agents when chemotherapy-related AEs appeared were shown in Supplementary Table 3. Dose adjustments in chemotherapy should be based on the maximum graded toxicity within the previous cycle. For patients who suffered from hematological toxicity and/or non-hematological toxicity for more than 21 days, chemotherapy should be discontinued unless the investigator and sponsor reached an agreement on continuation due to potential clinical benefit for patients. If a decrease in white blood cells or neutrophils of grade 3 or 4 emerged, chemotherapy should be withheld and the original dose could be maintained if it recovered to grade 1 or baseline level at 21 days. If febrile neutropenia occurred (neutrophils < 1000 per cubic millimeter, with fever of $\geq 38^\circ\text{C}$ for more than 1 h or a single temperature measurement of $> 38.3^\circ\text{C}$) or grade 4 neutropenia occurred repeatedly or for up to 7 days, dose reductions were required after recovering to grade 1 or baseline levels at 21 days. In addition, nausea, vomiting, or diarrhea was initially treated with supportive care, and if this was still unacceptable, chemotherapy was withheld until toxicity recovered to grade 1 or baseline levels. For the side effects that were considered by the investigators to be unlikely to develop into serious or life-threatening AEs (hyperuricemia, hypophosphatemia, alopecia, etc.) and could be tolerated by the patients, the chemotherapy could be maintained at the same dose level without dose reduction or interruption, as long as the patients were actively given symptomatic treatment.

Radiotherapy should be paused when there was grade 3 or higher radiation dermatitis in the radiation field and restarted when dermatitis recovered to grade 1 or greater. Radiotherapy should also be paused if any grade 4 AEs occurred and radiotherapy could be recontinued when the AEs recovered to grade 1 or greater. The prescribed dose of radiotherapy was not amended unless new AEs occurred or the original AEs were aggravated.

Radical surgery

Four weeks after the final cycle of preoperative chemotherapy combined with bispecific antibody

immunotherapy, a multidisciplinary team (MDT) meeting, including surgeon, radiation oncologist, medical oncologist, radiologist, pathologist and so forth, would be launched and image evaluation will be adopted for patients to confirm whether R0 resection was possible and if cCR criteria were reached. If R0 resection was feasible, surgery would be performed 28 days after the first day of the last administration of chemotherapy combined with bispecific antibody immunotherapy in the final course. If R0 resection was infeasible or disease progression was observed, the protocol treatment will be discontinued. The surgery must be a total mesorectal excision, and the exact procedure would be decided by the surgeon, including anterior resection (AR), laparoscopic resection (APR) or Hartmann's procedure. Extending 4 to 5 cm below the distal edge of tumors for an adequate mesorectal excision was needed. A negative margin of 1 to 2 cm for distal rectal cancers (< 5 cm from anal verge) was acceptable. For patients with suspicious lateral pelvic lymph node involvement, whether to perform extended resections beyond the TME plane depended on the actual situation and MDT advice. The expression of MMR protein and PD-1 immunohistochemical results should be described in the preoperative biopsy report. The postoperative pathological diagnosis should include the gross condition of the tumor, histological type and grade, treatment response, resection margin, lymph node metastasis, pathological stage and immunohistochemical results. If a patient reached the cCR criteria, the cCR follow-up strategy was carried out.

Follow-up after treatment completion

Patients would be followed up on a fixed schedule for at least three years after surgical completion. The first and second visits would be arranged 30 days and 90 days after resection to evaluate the safety and tolerability of treatment, and then every 3 months thereafter to document the survival outcome of each patient. See Supplementary Table 4 and Supplementary Table 5 for the schedule of evaluations after the completion of treatment. Each patient remained on study until disease progression, infeasibility of surgery after completion of neoadjuvant treatment, withdrawal of consent, unacceptable toxicity, pregnancy, loss of follow-up, or death. Patients with cCR after preoperative chemoradiotherapy and immunotherapy and then firmly choosing the wait and watch strategy would be followed up according to an intensively follow-up strategy in every 3 months requirement of comprehensive examination, including pelvic magnetic resonance imaging (MRI), computed tomography (CT) imaging, colorectal endoscopy, digital rectal examination and routine laboratory tests.

Data collection of QoL and rectal function

During the protocol treatment and follow-up period, the European Organization for Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30 [36, 37] and CR29 [38] were adopted as patient reported outcome measures (PROMs) to assess QoL at baseline, before and 1 month after surgery, and 6, 12, 24 and 36 months after surgery. The functional outcome of the rectum would be collected through the Wexner score [39] for patients who received sphincter-preserving surgery at the same time as the assessment of QoL. Specifically, for patients with cCR, QoL and functional outcome of the rectum 1 month after the date of confirming cCR would be collected, and an intensive every 3 months schedule of the assessment of QoL and functional outcome of the rectum would be carried out after the date of confirming cCR in the first year and then every 6 months in the second and third years.

Safety run-in analysis

Due to a lack of data about the safety profile of combining Cadonilimab with SCRT and chemotherapy for LARC, a safety run-in phase was conducted to evaluate the feasibility of the experimental treatment. A total of 6 patients were included according to the eligibility criteria. The safety profile was reviewed by an Independent Data Monitoring Committee (IDMC). It was gathered 28 days after the 6th patient received the first cycle of Cadonilimab plus chemotherapy. If the first 6 patients tolerated this combination treatment and no safety issues arose, the enrollment would be continued.

Statistical analysis for primary endpoint

Based on the results of a previous study [8], the objective of this study was to increase the complete remission rate from 21.8% to 40%. A Simon two-stage approach optimal design was used to yield a type-1 error of 0.05 and 80% power. The first phase would include 8 patients, plus 6 patients in the safety run-in period, for a total of 14 patients, and if ≥ 4 of these patients achieved a CR, the study would move into the second phase. Taking into account for a 10% drop-out rate, the total actual goal was 50 patients.

Following the intent-to-treat principle, the full analysis set, defined as all patients who received at least one dose of the study drug with measurable lesions at baseline according to RECIST v1.1, would be utilized to conduct the efficacy analysis. At the same time, the safety set, defined as all patients who received at least one dose of study drug according to the actual adoption of treatment for patients, would be utilized to conduct the safety analysis. Descriptive statistics would be conducted on

baseline characteristics, tumor response, biomarkers, and AEs. Survival curves would be plotted using the Kaplan–Meier method. The missing data would not be included in the final data analysis.

Monitoring

Regular monitoring would be performed annually by an IDMC to verify the protocol compliance, the accuracy and consistency of the data and the adherence to the International Conference on Harmonization–Good Clinical Practice (ICH–GCP) and local regulations when conducting the clinical study.

Status of the trial

This trial started in April 2023 and patient recruitment was ongoing on August 30, 2023.

Discussion

This study would provide evidence on the efficacy and safety of SCRT plus bispecific antibody immunotherapy combined with chemotherapy as neoadjuvant therapy for patients with LARC, which might be used as a candidate potential therapy in the future.

A preclinical study showed that the immune response induced by radiation might be dose-dependent [40]. The immune response induced by high-dose irradiation was different from that induced by conventionally fractionated irradiation. High dose irradiation could induce the activation of the death receptor Fas signaling pathway, which rendered irradiated cells susceptible to killing by cytotoxic lymphocytes [41]. Reits et al. [42] found that ≥ 10 Gy radiation could increase the expression of MHC-1 and induce an antitumor immune response in mice with colon cancer. A recent randomized phase II trial showed that, compared to stereotactic ablative radiotherapy (SABR) alone, SABR combined with immunotherapy could significantly improve event-free survival from 53 to 77% in early-stage non-small cell lung cancer [43]. As the radiation dose increased, this phenomenon might be more obvious while low-dose radiation had no such effect. The upregulation in MHC-1 expression induced by high-dose radiation was due to the induction and activation of mammalian target of rapamycin (mTOR), since rapamycin (an mTOR inhibitor) could reduce the radiation-induced high expression of MHC-1. The application of SCRT in this study might be able to further promote the immune response and tumor regression.

The utilization of dual immunotherapy was a potential research direction for improving the prognosis of various types of solid tumors. The CheckMate 067 trial had shown a superior clinical benefit in advanced melanoma patients treated by nivolumab plus ipilimumab with a

median OS of 72.1 months compared to nivolumab alone or ipilimumab alone [44]. Furthermore, a durable clinical outcome after the administration of dual immunotherapy was observed in patients with recurrent small cell lung cancer or metastatic urothelial carcinoma in the CheckMate 032 trial [45, 46]. Specifically, the results from a phase Ia/Ib study of an anti-CTLA-4 monoclonal antibody, plus an anti-PD-1 antibody in metastatic microsatellite stable (MSS) CRC yielded an objective response rate of 22% [47], while previous clinical studies had shown that MSS CRC did not benefit much from immunotherapy as a single agent [48]. For mCRC patients with MSI-H/dMMR, the anti-CTLA-4 plus anti-PD-1 regimen from the CheckMate 142 study was also better than the single anti-PD-1 regimen from the KEYNOTE 177 study [49, 50]. Regardless of microsatellite status, dual immunotherapy regimens might be more effective than monotherapy.

It was one of our main concerns that whether the addition of bispecific antibody into SCRT in this study increases adverse events. A phase Ib/II, multicenter study recently updated their two-year data of an ORR of 68.2%, with 5 (5.7%) complete responses and 55 (62.5%) partial responses in advanced gastric or gastroesophageal junction cancer patients treated with Cadonilimab and chemotherapy [51]. Grade ≥ 3 treatment-related adverse events occurred in 69.4% of patients, most of which were myelosuppression and gastrointestinal reactions without new safety signals identified. This preferable treatment outcome was replicated in advanced cervical cancer with an ORR of 68–92% and grade ≥ 3 treatment-related toxicity, mainly consisting of hematological toxicity, occurred in 51.1% of patients, whose grade ≥ 3 irAEs were reported with an incidence of 17.8% [52]. Based on the results, the treatment-related toxicity of adding Cadonilimab, into TNT was considered manageable and acceptable.

In summary, the combination with radiotherapy had the potential to improve the efficacy of immune checkpoint inhibitors. Therefore, the addition of bispecific antibodies to SCRT in the treatment strategy of TNT was worthy of further exploration of the rate of complete response and prognosis for LARC patients. We looked forward to obtaining better results and selecting a better treatment strategy.

Abbreviations

LARC	Locally Advanced Rectal Cancer
CRC	Colorectal Cancer
CRT	Chemoradiotherapy
TME	Total Mesorectal Excision
SCRT	Short-Course Radiotherapy
TNT	Total Neoadjuvant Therapy
CR	Complete Response
pCR	Pathological Complete Response
cCR	Clinical Complete response
LRFS	Local–Regional Recurrence-Free Survival

DMFS	Distant Metastasis-Free Survival
DFS	Disease-Free Survival
OS	Overall Survival
MHC	Major Histocompatibility Complex
dMMR	Deficient Mismatch Repair
MSI-H	Microsatellite Instability-High
CTLA-4	Cytotoxic T-Lymphocyte Antigen-4
PD-1	Programmed Cell Death Protein-1
ORR	Objective Response Rate
RECIST	Response Evaluation Criteria in Solid Tumors
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
AEs	Adverse Events
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
QoL	Quality of Life
CAPOX	Capecitabine, Oxaliplatin
FOLFOX	5-Fluorouracil, Oxaliplatin
IMRT	Intensity Modulated Radiation Therapy
VMAT	Volume Modulated Arc Therapy
TOMO	Tomotherapy
CTV	Clinical Target Volume
PTV	Planning Target Volume
irAEs	Immune-Related Adverse Events
MDT	Multidisciplinary Team
AR	Anterior Resection
APR	Laparoscopic Resection
MRI	Magnetic Resonance Imaging
DWI	Diffusion Weighted Imaging
CT	Computed Tomography
IDMC	Independent Data Monitoring Committee
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
SABR	Stereotactic Ablative Radiotherapy
mTOR	Mammalian Target of Rapamycin
MSS	Microsatellite Stable
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
TBIL	Total Bilirubin
HIV	Human Immunodeficiency Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12885-024-12254-1>.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Acknowledgements

Not applicable.

Authors' contributions

All authors have read and approved the manuscript before submission. JJ and YT designed the research study. JJ, YT, YGC, HTZ, TZX, LLF, WJZ, HYL, HYM, MA, YTT, FYD, WTH, SMZ, WYK, LMJ, and YW performed the research. CH provided help and advice on the research. TZX and LLF wrote the manuscript. JJ, YT, YGC and HTZ revised the manuscript.

Funding

The project is supported by the National Natural Science Foundation of China (82073352) and National Cancer Center/National Clinical Research Center for

Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen (E010121001). And the funding bodies' support is primarily financial.

Availability of data and materials

The datasets used and/or analyzed during the current study were available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study (Protocol version 2.0, October 8, 2022) was approved by the Ethics Committee of the Cancer Hospital&Shenzhen Hospital Chinese Academy of Medical Sciences (YW2022-21-3) and the Cancer Hospital Chinese Academy of Medical Sciences (23/283-4025). It was registered at Clinicaltrials.gov (NCT05794750) with the name "Assess the Efficacy of Radiotherapy and Sequential Chemotherapy and AK104 Before TME Surgery for Local CRC (AK104-IIT-13)". The study protocol had been approved by all participant centers. The principal investigator was responsible for submitting the protocol amendments and changes to the informed consent document to the Institutional Review Board(s) and/or Independent Ethics Committee(s) at each center and obtaining their approval where necessary. If substantial amendments to the protocol and other relevant study documents were required, the principal investigator would ensure that they were implemented only after approval by the relevant regulatory authorities. The Human Ethics Committee of the Cancer Hospital and Shenzhen Hospital Chinese Academy of Medical Sciences and the Cancer Hospital Chinese Academy of Medical Sciences had granted central ethical approval. All personnel involved in conducting the current study should abide by the latest Declaration of Helsinki and Ethical Guidelines for Clinical Studies. Written informed consent would be obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹State Key Laboratory of Molecular Oncology and Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. ²Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen 518116, China. ³Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen 518116, China. ⁴State Key Laboratory of Molecular Oncology and Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. ⁵Department of Radiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen 518116, China. ⁶State Key Laboratory of Molecular Oncology and Department of Radiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. ⁷Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen 518116, China. ⁸Division of Biostatistics and Bioinformatics, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, USA. ⁹Department of Colorectal Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen 518116, China. ¹⁰State Key Laboratory of Molecular Oncology and Department of Colorectal Surgery, National Cancer Center/National

Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China.

Received: 24 September 2023 Accepted: 11 April 2024

Published online: 19 April 2024

References

- Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, Graeven U, Arnold D, Lang-Welzenbach M, Raab HR, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. *Lancet Oncol.* 2012;13(7):679–87.
- Fokas E, Schlenska-Lange A, Polat B, Klautke G, Grabenbauer GG, Fietkau R, Kuhnt T, Staib L, Brunner T, Grosu AL, et al. Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Patients With Locally Advanced Rectal Cancer: Long-term Results of the CAO/ARO/AIO-12 Randomized Clinical Trial. *JAMA Oncol.* 2022;8(1):e215445.
- Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol.* 2012;30(16):1926–33.
- van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van de Velde CJ. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol.* 2011;12(6):575–82.
- Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, Quirke P, Couture J, de Metz C, Myint AS, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet.* 2009;373(9666):811–20.
- Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, Vendrely V, Artignan X, Bouché O, Gargot D, 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):702–15.
- Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM, Roodvoets AGH, Nagtegaal ID, Beets-Tan RGH, Blomqvist LK, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22(1):29–42.
- Jin J, Tang Y, Hu C, Jiang LM, Jiang J, Li N, Liu WY, Chen SL, Li S, Lu NN, et al. Multicenter, Randomized, Phase III Trial of Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer (STELLAR). *J Clin Oncol.* 2022;40(15):1681–92.
- Wang Y, Liu ZG, Yuan H, Deng W, Li J, Huang Y, Kim BYS, Story MD, Jiang W. The Reciprocity between Radiotherapy and Cancer Immunotherapy. *Clin Cancer Res.* 2019;25(6):1709–17.
- Mouw KW, Goldberg MS, Konstantinopoulos PA, D'Andrea AD. DNA Damage and Repair Biomarkers of Immunotherapy Response. *Cancer Discov.* 2017;7(7):675–93.
- Jiang W, Chan CK, Weissman IL, Kim BYS, Hahn SM. Immune Priming of the Tumor Microenvironment by Radiation. *Trends Cancer.* 2016;2(11):638–45.
- Zheng X, Fang Z, Liu X, Deng S, Zhou P, Wang X, Zhang C, Yin R, Hu H, Chen X, et al. Increased vessel perfusion predicts the efficacy of immune checkpoint blockade. *J Clin Invest.* 2018;128(5):2104–15.
- Tamberi S, Grassi E, Zingaretti C, Papianni G, Pini S, Corbelli J, Di Bartolomeo M, Pietrantonio F, Frassinetti GL, Passardi A, et al. A phase II study of capecitabine plus concomitant radiation therapy followed by durvalumab (MED14736) as preoperative treatment in rectal cancer PANDORA study final results. *J Clin Oncol.* 2022;40(17Suppl):LBA3513–LBA3513.
- Rahma OE, Yothers G, Hong TS, Russell MM, You YN, Parker W, Jacobs SA, Colangelo LH, Lucas PC, Gollub MJ, 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):8–8.
- Carrasco J, Schröder D, Sinapi I, De Cuyper A, Beniuga G, Delmarcelle S, Van Laethem JL, Huyghe N, Bar I, Hendlisz A, et al. 397P RIMMUNE interim analysis A phase Ib/II study to evaluate safety and efficacy of atezolizumab combined with radio-chemotherapy in a preoperative setting for patients with localized rectal cancer. *Annals Oncol.* 2021;32:537.
- Glynn-Jones R, Hall M, Nagtegaal ID. The optimal timing for the interval to surgery after short course preoperative radiotherapy (5 x5 Gy) in rectal cancer - are we too eager for surgery? *Cancer Treat Rev.* 2020;90:102104.
- Shamseddine A, Machmouchi A, Natout M, Turfa R, Kattan JG, Temraz SN, Tawil A, Elkhalidi M, Jaber O, Amarin R, et al. Assessment of Immunoscore and MRI tumor regression grade to predict complete pathologic response in patients with locally advanced rectal cancer: Data from phase II Averecal study. *J Clin Oncol.* 2023;41(4Suppl):212–212.
- Lin Z, Cai M, Zhang P, Li X, Cai K, Nie X, Tao K, Zhang T. Short-course radiotherapy and subsequent CAPOX plus camrelizumab followed by delayed surgery for locally advanced rectal cancer: Short-term results of a phase II trial. *J Clin Oncol.* 2021;39(3):63–63.
- Lenz HJ, Van Cutsem E, Luisa Limon M, Wong KYM, Hendlisz A, Aglietta M, Garcia-Alfonso P, Neyns B, Luppi G, Cardin DB, et al. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer The Phase II CheckMate 142 Study. *J Clin Oncol.* 2022;40(2):161–70.
- Thibaudin M, Fumet JD, Chibaudel B, Bennouna J, Borg C, Martin-Babau J, Cohen R, Fonck M, Taieb J, Limagne E, et al. First-line durvalumab and tremelimumab with chemotherapy in RAS-mutated metastatic colorectal cancer: a phase 1b/2 trial. *Nat Med.* 2023;29(8):2087–98.
- Chalabi M, Fanchi LF, Dijkstra KK, Van den Berg JG, Aalbers AG, Sikorska K, Lopez-Yurda M, Grootsholten C, Beets GL, Snaebjornsson P, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med.* 2020;26(4):566–76.
- Motzer RJ, Rini BI, McDermott DF, Arén-Frontera O, Hammers HJ, Carducci MA, Salman P, Escudier B, Beuselinck B, Amin A, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2019;20(10):1370–85.
- Keam SJ. Cadonilimab: first approval. *Drugs.* 2022;82(12):1333–9.
- Millward M, Frentzas S, Gan HK, Prawira A, Tran B, Coward J, Jin X, Li B, Wang M, Kwek KY, et al. 1021O Safety and antitumor activity of AK104, a bispecific antibody targeting PD-1 and CTLA-4, in patients with mesothelioma which is relapsed or refractory to standard therapies. *Ann Oncol.* 2020;31:5705–6.
- Gao X, Xu N, Li Z, Shen L, Ji K, Zheng Z, Liu D, Lou H, Bai L, Liu T, et al. Safety and antitumor activity of cadonilimab, an anti-PD-1/CTLA-4 bispecific antibody, for patients with advanced solid tumours (COM-PASSION-03): a multicentre, open-label, phase 1b/2 trial. *Lancet Oncol.* 2023;24(10):1134–46.
- Ji J, Shen L, Li Z, Gao X, Xia Y. 840TIPA phase Ib/II study of AK104, a PD-1/CTLA-4 bispecific antibody, combined with mXELOX as first-line therapy for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. *Ann Oncol.* 2019;30(Supplement_5):V323–4.
- Wu L, Chen B, Yao W, Li X, Xiao Z, Liu H, Kong Y, Liu L, Xu Y, Wang Q, et al. 1300P A phase Ib/II trial of AK104 (PD-1/CTLA-4 bispecific antibody) in combination with anlotinib in advanced NSCLC. *Ann Oncol.* 2021;32:51006.
- Bai L, Sun M, Xu A, Bai Y, Wu J, Shao G, Song L, Jin X, Song W, Li B, et al. Phase 2 study of AK104 (PD-1/CTLA-4 bispecific antibody) plus lenvatinib as first-line treatment of unresectable hepatocellular carcinoma. *J Clin Oncol.* 2021;39(15):4101–4101.
- Zhao Y, Ma Y, Fan Y, Zhou J, Yang N, Yu Q, Zhuang W, Song W, Wang ZM, Li B, et al. A multicenter, open-label phase Ib/II study of cadonilimab (anti PD-1 and CTLA-4 bispecific antibody) monotherapy in previously treated advanced non-small-cell lung cancer (AK104-202 study). *Lung Cancer.* 2023;184:107355.

30. Wu X, Ji J, Lou H, Li Y, Feng M, Xu N, Li Y, Wang J, Huang Y, Lou G, et al. Efficacy and safety of cadonilimab, an anti-PD-1/CTLA4 bi-specific antibody, in previously treated recurrent or metastatic (R/M) cervical cancer: a multicenter, open-label, single-arm, phase II trial (075). *Gynecol Oncol*. 2022;166:547–8.
31. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancy J, Arbuck S, Gwyther S, Mooney M, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–47.
32. U.S. National Institutes of Health, N.C.I. *Common Terminology Criteria for Adverse Events (CTCAE) version 5.0*. 2017 Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Cited 2023 July 1
33. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649–55.
34. Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, van Dam RM, Jansen RL, Sosef M, Leijtens JW, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol*. 2011;29(35):4633–40.
35. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714–68.
36. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365–76.
37. Fayers PMAN, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group, *The EORTC QLQ-C30 Scoring Manual (3rd Edition)*. Brussels: Published by: European Organisation for Research and Treatment of Cancer; 2001.
38. Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M, Johnson CD, Pilkington SA, Arraras J, Ben-Josef E, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. *Eur J Cancer*. 2009;45(17):3017–26.
39. Jorge MJN, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum*. 1993;36(1):77–97.
40. Schaeue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys*. 2012;83(4):1306–10.
41. Chakraborty M, Abrams SI, Coleman CN, Camphausen K, Schlom J, Hodge JW. External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated T-cell killing. *Cancer Res*. 2004;64(12):4328–37.
42. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, Camphausen K, Luiten RM, de Ru AH, Neijssen J, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med*. 2006;203(5):1259–71.
43. Chang JY, Lin SH, Dong W, Liao Z, Gandhi SJ, Gay CM, Zhang J, Chun SG, Elamin YY, Fossella FV, et al. Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial. *Lancet*. 2023;402(10405):871–81.
44. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Lao CD, Cowey CL, Schadendorf D, Wagstaff J, Dummer R, et al. Long-term outcomes with Nivolumab Plus Ipilimumab or Nivolumab Alone Versus ipilimumab in patients with advanced Melanoma. *J Clin Oncol*. 2022;40(2):127–37.
45. Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, Antonia SJ, Ascierto PA, Moreno V, Atmaca A, et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in recurrent small cell lung cancer: results from the checkmate 032 randomized cohort. *J Thorac Oncol*. 2020;15(3):426–35.
46. Sharma P, Siefker-Radtke A, Braud FD, Basso U, Calvo E, Bono P, Morse MA, Ascierto PA, Lopez-Martin J, Brossart P, et al. Nivolumab alone and with ipilimumab in previously treated metastatic Urothelial Carcinoma CheckMate 032 Nivolumab 1 mg/kg Plus Ipilimumab 3 mg/kg expansion cohort results. *J Clin Oncol*. 2019;37(19):1608–16.
47. El-Khoueiry AB, Fakih M, Gordon MS, Tsimberidou AM, Bullock AJ, Wilky BA, Trent JC, Margolin KA, Mahadevan D, Balmanoukian AS, et al. Results from a phase 1a/1b study of botensilimab (BOT), a novel innate/adaptive immune activator, plus balstilimab (BAL; anti-PD-1 antibody) in metastatic heavily pretreated microsatellite stable colorectal cancer (MSS CRC). *J Clin Oncol*. 2023;41(4 suppl):LBA8–LBA8.
48. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Lubner BS, Azad NS, Laheru D, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med*. 2015;372(26):2509–20.
49. Overman MJ, Lonardi S, Wong KYM, Lenz H-J, Gelsomino F, Aglietta M, Morse MA, Cutsem EV, McDermott R, Hill A, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/ Microsatellite Instability-High Metastatic Colorectal Cancer. *J Clin Oncol*. 2018;36(8):773–9.
50. Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, El Dika IH, Segal N, Shcherba M, Sugarman R, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *N Engl J Med*. 2022;386(25):2363–76.
51. Ji J, Shen L, Li Z, Gao X, Ji K, Chen Y, Xu N, Liu T, Yang N, Zhong H, et al. A phase Ib/II, multicenter, open-label study of AK104, a PD-1/CTLA-4 bispecific antibody, combined with chemotherapy (chemo) as first-line therapy for advanced gastric (G) or gastroesophageal junction (GEJ) cancer: 2-Year update data. *Journal of Clinical Oncology*. 2023;41(16 suppl):4031–4031.
52. Wang J, Lou H, Cai H-B, Huang X, Li G, Wang L, Liu T, Liu W, Li B, Xia Y. A study of AK104 (an anti-PD1 and anti-CTLA4 bispecific antibody) combined with standard therapy for the first-line treatment of persistent, recurrent, or metastatic cervical cancer (R/M CC). *J Clin Oncol*. 2022;40(16 suppl):106–106.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.