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Immunotherapy in the neoadjuvant treatment of gastrointestinal tumors: is the time ripe?

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ABSTRACT

Immune checkpoint inhibitors (ICIs) revolutionized the management of mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) gastrointestinal (GI) cancers. Based on notable results observed in the metastatic setting, several clinical trials investigated ICIs as neoadjuvant treatment (NAT) for localized dMMR/MSI-H GI cancers, achieving striking results in terms of clinical and pathological responses and creating the opportunity to spare patients from neoadjuvant chemotherapy and/or radiotherapy and even surgical resection. Nevertheless, these impressive findings are mainly derived from small proof of concept phase II studies and there are still several open questions to address. Moreover, dMMR/MSI-H represents a limited subgroup accounting for less than 10% of GI cancers. Consequently, many efforts have been produced to investigate neoadjuvant ICIs also in mismatch repair-proficient/microsatellite stable (MSS) cancers, considering the potential synergistic effect in combining immune-targeted agents with standard therapies such as chemo and/or radiotherapy. However, results for combining ICIs to the standard of care in the unselected population are still unsatisfactory, without improvements in event-free survival in esophago-gastric adenocarcinoma for the addition of pembrolizumab to chemotherapy, and sometimes limited benefit in patients with locally advanced rectal cancer. Therefore, a major challenge will be to identify among the heterogenous spectrum of this disease, those patients that could take advantage of neoadjuvant immunotherapy and deliver the most effective treatment. In this review we discuss the rationale of NAT in GI malignancies, summarize the available evidence regarding the completed trials that evaluated this treatment strategy in both MSI-H and MSS tumors. Finally, we discuss ongoing studies and future perspectives to render neoadjuvant immunotherapy another arrow in the quiver for the treatment of locally advanced GI tumors.

INTRODUCTION

Over the last decades, immunotherapy, and specifically immune checkpoint inhibitors (ICIs), has become one of the pillars of cancer treatment, with increasing applications in different malignancies, both in palliative and in the curative setting. As for gastrointestinal (GI) cancers, including esophageal, gastric and colorectal, ICIs have been approved by Food and Drug Agency only in the metastatic setting, including pembrolizumab for first-line deficient mismatch repair (dMMR)/microsatellite high (MSI-H) colorectal cancer (CRC), nivolumab +/− ipilimumab for second-line for dMMR/MSI-H CRC, nivolumab plus chemotherapy for first-line esophago-gastric cancer (EGC), pembrolizumab for pretreated patients with programmed death-ligand 1 (PD-L1) positive EGC, nivolumab +/− chemo or ipilimumab for first-line esophageal squamous cell cancers (ESCC) irrespective of PD-L1 status, pembrolizumab for pretreated dMMR/MSI-H cancers (including EGC, biliary tract and small bowel cancers).[1–6] Similar approvals have been granted by the European Medicines Agency, with some limitations for the use of nivolumab in addition to chemotherapy/ipilimumab for first-line EGC and ESCC, according to PD-L1 expression.[7]

Based on this promising background, ICIs have been widely investigated as part of multimodal treatments in locally advanced (LA) cancer. In this context, GI cancers represent an ideal clinical setting to test ICIs since neoadjuvant treatment (NAT) represents the current standard approach for LA EGC and rectal cancer.[8–10] Several studies have been published, and others are ongoing, although no ICI approval occurred in NAT yet. In this review, we will focus exclusively on the use of ICIs in the neoadjuvant setting of EGC and CRC, by critically reviewing the current evidence and addressing future development in the field.

Principle of immunotherapy

ICIs have revolutionized the cancer treatment scenario by prolonging the survival of patients. It is focused on the development of agents able to stimulate or suppress the

immune system, in a specific manner, to fight off a wide spectrum of diseases, including cancers.[11] Immune cells recognize and eliminate tumor cells, inhibiting cancer development and progression. However, studies made throughout the past two decades have demonstrated that our immune system can paradoxically limit and promote tumor development and progression.[12 13] This specific process is referred to "cancer immune editing" and consists of three different phases: elimination, equilibrium, and escape.[14] Innate and adaptive immune systems cooperate to recognize and destroy cancer cells in the elimination phase. Second, the equilibrium phase is mediated by the adaptive immune system, preventing tumor cells development, and it is also characterized by some rare tumor cell variants that survived to the elimination phase. Finally, immunologically sculpted tumors gain the ability to survive immune surveillance and progressively grow establishing an immunosuppressive tumor microenvironment and lastly, becoming clinically apparent.[15]

Notably, cancer cells are surrounded by many cell types including immune cells which constitute the tumor immune microenvironment whose composition, location and density are now recognized to be prognostic for patients' survival and predictive for responses to treatment.[16] Otherwise, several immune escape mechanisms have been identified: a reduced immune recognition due to the lack of specific antigens or alterations in their presentation, the promotion of an immune tolerant microenvironment formation affecting cytokine levels, and the upregulation of immune-checkpoint molecules such as programmed cell death 1 (PD-1) or PD-L1 (figure 1). In fact, immune response is finely regulated at multiple levels, which act as checkpoints and negatively downregulate T-cell activation, to preserve self-tolerance.[17]

Cytotoxic T lymphocyte antigen 4 (CTLA4) and PD-1 are considered the two main immune checkpoint receptors in cancer. Their discovery led to the development of ICIs, which have shown clinical efficacy in many cancer types. By blocking the interaction between immune cells and tumor cells, ICIs enable T cells to recognize tumor antigens and destroy cancer cells.[16] Conversely, to classic cytotoxic treatments, ICIs can induce durable responses even after treatment discontinuation. This occurrence has been observed, for instance, in patients with

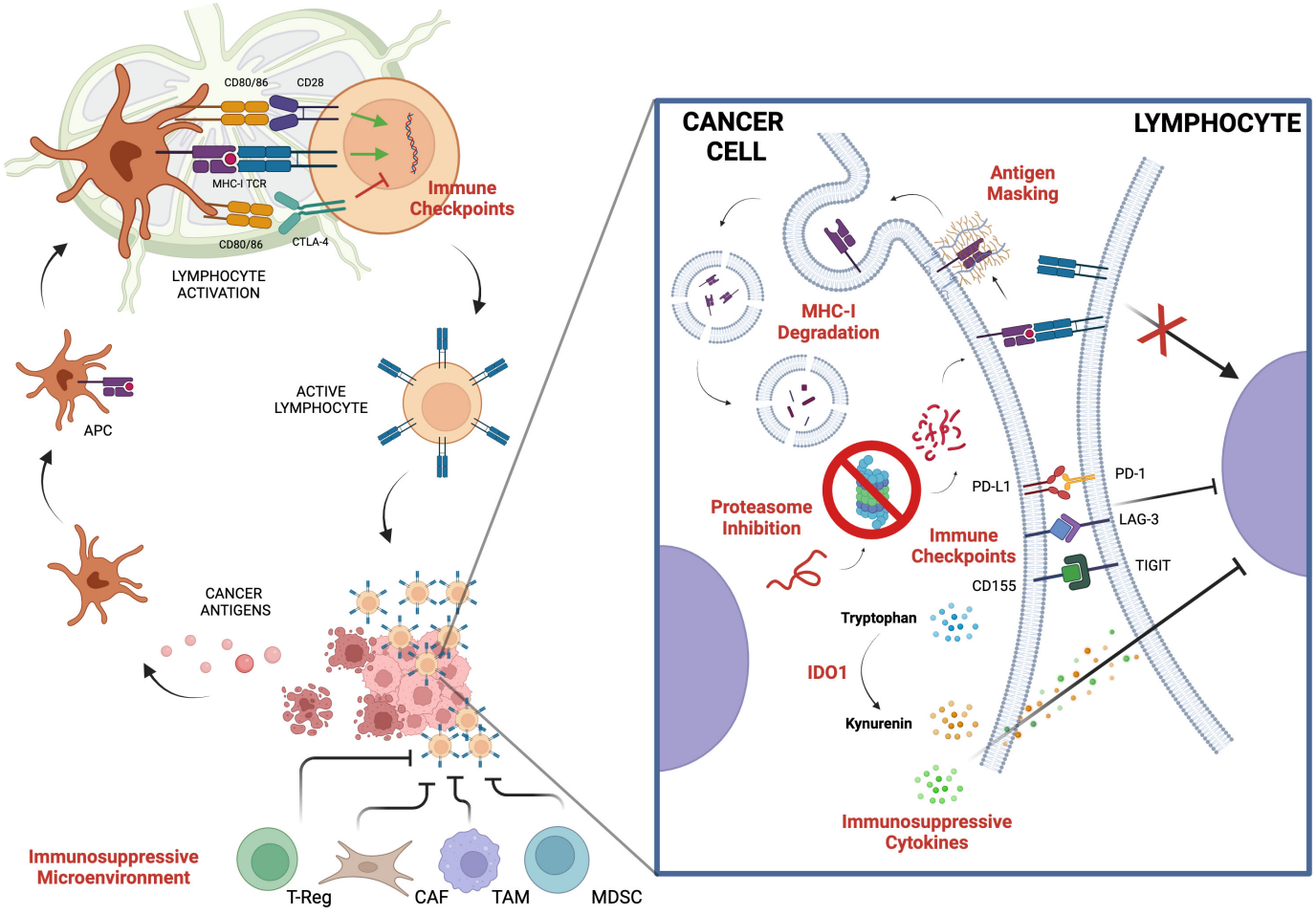

Figure 1 Key biologic mechanisms of cancer immune escaping. APC, antigen presenting cell; CAF, cancer-associated fibroblasts; CTLA4, cytotoxic T lymphocyte antigen 4; IDO1, indoleamine 2,3-dioxygenase; LAG3, lymphocyte-activation gene 3; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; TAM, tumor-associated macrophages; TCR, T-cell receptor; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; T-reg: regulatory T Cell

advanced-stage melanoma treated with the anti-CTLA4 antibody ipilimumab, where a meaningful proportion of patients reached a plateau in overall survival (OS) approximately 3 years after treatment initiation.[18]

Neoadjuvant ICI therapy: rationale and clinical development

NAT refers to the systemic and/or locoregional treatment of LA radically resectable cancer performed before surgery. It usually consists of chemotherapy (CT), radiotherapy (RT) or a combination of both (chemoradiotherapy, CRT). The key principles behind NAT administration include an increased probability of achieving tumor downsizing with a possible safer surgical approach, higher rates of radical resections with microscopical negative residual disease (R0), and improvement in survival given its potentiality in eradicating distant micrometastases.[19] Furthermore, NAT may lead to pathologic complete response (pCR) which could be associated with improved disease-free survival (DFS), or OS as reported for many types of cancer.[20] Another potential advantage of NAT is that it could induce a strong translational impact allowing testing of in vivo tumor biology response.

Immunotherapy has been reported to be biologically more effective as neoadjuvant rather than adjuvant treatment (figure 2). In preclinical models, CD8+T cells levels were significantly higher in both peripheral blood and organs, demonstrating stronger T-cell proliferation in the pre-surgical stage. One of the reasons potentially implicated in these results is linked to a higher release of tumor-specific antigens when primary tumor cells are exposed to ICIs. This may induce a strong vaccine effect on the immune system inducing an expansion of intratumoral tumor-specific T cells before they are released into the periphery.[21] This evidence was confirmed in the clinical setting: Blank *et al*[22] showed the improved effect of neoadjuvant administration immunotherapy compared with adjuvant immunotherapy in melanoma.[21]

Immunotherapy has been extensively studied in GI cancers, particularly after the identification of distinct subsets based on microsatellite status. Microsatellite

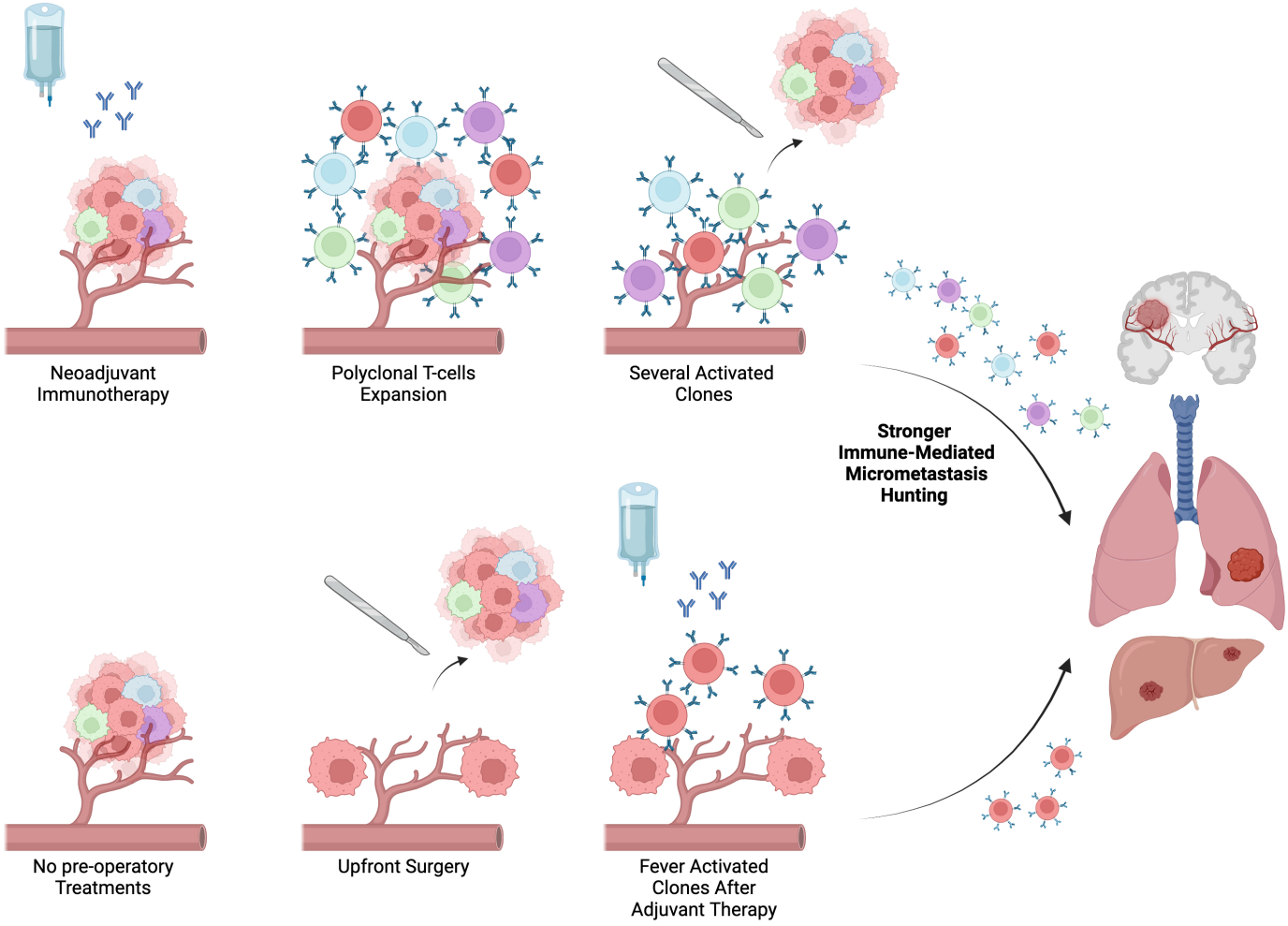

Figure 2 Biologic rational for the use of immune checkpoint inhibitors in neoadjuvant setting compared with upfront surgery and adjuvant chemotherapy APC, antigen presenting cell; CAF, cancer-associated fibroblasts; CTLA-4, cytotoxic T-lymphocyte antigen 4; IDO1, indoleamine 2,3-dioxygenase; LAG-3: lymphocyte-activation gene 3; MDSC, myeloid-derived suppressor cells; MHC-I, major histocompatibility complex class I; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; TAM, tumor-associated macrophages; TCR, T-cell receptor; TIGIT, T-cell immunoreceptor with Ig and ITIM domains.

instability (MSI) is a condition defined by hypermutability of the repetitive sequences scattered along the genome, called microsatellites. This condition is an expression of an underlying dMMR, which translates into genome-wide hypermutability.[23] dMMR cancers harbor up to 100 times more mutations than the mismatch repair proficient (pMMR) ones, resulting in a highly immunogenic profile.[6] In support of this hypothesis is the finding that MSI-high (MSI-H) cancers present a much higher number of infiltrating lymphocytes as well as intratumoral expression of immune checkpoints as a mechanism to inhibit immune-mediated tumor killing.[24] Therefore, MSI-H cancers have been hypothesized to be more sensitive to immune system reactivation through ICIs. For those reasons, distinctions should be made between pMMR/microsatellite stable (MSS) and dMMR/MSI-H cancers in relation to both immunogenicity and chemo-refractoriness.

Neoadjuvant ICIs in radically resectable locally advanced lower-GI cancers

Rectal cancer

Treatment of locally advanced rectal cancer (LARC) requires a multidisciplinary approach with NAT. Conventional short-course radiotherapy (SCRT) (five fractions of 5 Gy over 5 days) or concomitant long-course CRT and delayed surgery lead approximately 10% of patients to obtain a pCR[10 25] at surgical resection. In the case of total neoadjuvant treatment (TNT), that is a combination of systemic CT and CRT, an increased response rate (RR) was observed, with up to 30% of pCR according to prospective trials.[26 27] Recently, a watch and wait strategy has been proposed for selected patients who obtained a complete clinical (radiological/endoscopic) tumor response after NAT reserving rescue surgery in case of local recurrence.[28] Of course, this conservative treatment is particularly acceptable for the subset of patients with distal LARC to avoid colostomy. Therefore, novel therapeutic strategies to improve the complete response (CR) to allow a non-operative management allowing the organ preservation and reduce the risk of local/distal recurrence are warranted.

dMMR/MSI-H rectal cancer

ICIs are the standard of care for dMMR/MSI-H metastatic CRC and lead to deep and durable response.[1 2 29 30] Thus, there is a strong rationale for the use of ICIs in earlier settings including LARC (table 1).

The frequency of dMMR/MSI-H status is lower in rectal cancer (RC) compared with colon cancer (CC). In a large population including more than 5000 cases of RC dMMR/MSI-H was observed in 2.7% of tumor samples (147/5547).[31] In this scenario, Cercek reported impressive results of NAT with the anti-PD-1 dostarlimab in a population of dMMR/MSI-H LARC.[32] Overall, 12 patients with stage II/III MSI-H were enrolled and were candidate to receive 6 months of dostarlimab followed by CRT and surgery. In the case of clinical CR (cCR) after dostarlimab CRT and surgery could be avoided. Fascinatingly, at the time of the first report all 12 patients obtained a cCR after 6 months of dostarlimab and no sign of recurrence was observed at the first data cut-off. The trial is ongoing and still recruiting, and mature data with a longer follow-up are awaited. Similarly, NAT with four sintilimab was investigated in a population of Chinese patients with dMMR LARC.[33] Overall, six patients were treated with radical surgery, in no cases RT or CT was administered. Remarkably, clinical, or pCR was observed in 12 out 16 patients (75%), only in one case (6%) tumor enlargement was reported. In a case series of LA MSI-H CRC, 73 patients were treated with neoadjuvant ICIs. In the subgroup with rectal cancer 17/18 (94.4%) had pCR or partial response (PR).[34] All together, these findings strongly support the use of neoadjuvant ICIs in dMMR/MSI-H LARC with organ sparing in most cases, reserving surgery in case of persistent/progressive disease. The major limitation of these prospective/retrospective studies is the small number of patients included and relatively short follow-up, therefore larger prospective studies and longer follow-up are warmly waited (table 2).

pMMR/MSS rectal cancer

To date, ICIs demonstrated limited efficacy in advanced MSS CRC, therefore novel and more effective combinatory strategies are under investigation.[35] It has been shown that RT could elicit an immune modulatory effect. The “abscopal effect” is a rare phenomenon described for the first time in 1953.[36] It consists of tumor regression in a site distant from the field of irradiation. This may be due to the reactivation of the host immune response against cancer cells. Indeed, RT can increase the expression of major histocompatibility complex class I on cell membranes, and, thus, can improve antigen presentation by dendritic cells with a strong immune activation and subsequent immunogenic cell death.[37] Therefore, there is a strong rationale for combining RT and ICIs. AVERECTAL is a phase II single-arm study investigating the role of SCRT, followed by six cycles of mFOLFOX-6 plus the anti PD-L1 avelumab and total mesorectal excision as TNT for LARC.[38] Final results showed that 37.5% of patients achieved a pCR, while another 30% had a near-CR. Similar results were reported by two phase II study investigating SCRT followed by CAPOX plus the anti PD-1 camrelizumab or toripalimab and delayed surgery.[31 39]

A different treatment strategy is represented by a combination of CRT with immunotherapy. In the phase II AVANA trial, addressing the combination of avelumab plus CRT in patients with LARC, 23% of patients had a pCR and 61.5% a major pathological response (MPR).[40] In the PANDORA study, 55 patients with LARC received CRT followed by three cycles of durvalumab and surgery with a CR of 32.7%.[41] Conversely, negative results came up from the NRG-GI002 trial, in which 185 patients with LARC were treated with four cycles of FOLFOX followed by CRT with/without pembrolizumab before surgery[42]

Table 1 Completed studies of neoadjuvant immunotherapy in colorectal cancer

Trial number	Phase	Sample size	Treatments	Outcomes
NCT04165772	Single arm phase II	12	Dostarlimab9 cycles > CRT > Surgery	CR: 100%
NCT04304209	Single arm phase II	17	Sintilimab 4 cycles > sintilimab 4 cycles > W&W/surgery Or Sintilimab 4 cycles > surgery > CAPOX +/– sintilimab	CR: 75% PD: 6%
Xaio *et al*	Retrospective	73	ICIs > surgery ICIs > W&W	ORR: 84.9% (CR: 23.3%; PR: 61.6%) pCR: 57%
Zhang *et al*	Retrospective	32	ICIs > surgery ICIs > W&W	cCR: three patients MPR: 86.2% pCR:75%
Trojan *et al*	Case report	1	Nivolumab + ipilimumab 1 cycles	CR: 100%
Averectal (NCT03503630)	Single arm phase II	44	SCRT > FOLFOX + avelumab 6 cycles > surgery	pCR: 37.5%
NCT04231552	Single arm phase II	30	SCRT> CAPOX + camrelizumab 2 cycles > surgery	pCR: 100% (MSI-H) pCR: 46.2% (MSS)
TORCH (NCT04518280)	Randomized non-comparative phase II study	11	SCRT > CAPOX + camrelizumab 6 cycles > surgery/W&W Or CAPOX + camrelizumab 2 cycles > SCRT > CAPOX + camrelizumab 4 cycles > surgery/W&W	cCR: two patients pCR: 77.8%
AVANA (NCT03854799)	Single arm phase II	101	CRT + avelumab > avelumab (up to 6 cycles) > surgery	pCR: 22% (ITT population) pCR: 8% (MSS)
VOLTAGE-A (NCT02948348)	Single arm phase II	42	CRT + nivolumab > nivolumab (up to 5 cycles) > surgery	pCR: 60% (MSI-H) pCR: 30% (MSS)
PANDORA (NCT04083365)	Single arm phase II	26	CRT > durvalumab 3 cycles > surgery	pCR: 50%
NCT04911517	Single arm phase II	26	CRT + tislelizumab > surgery	pCR: 50%
NRG-GI002 (NCT02921256)	Randomized phase II	180	FOLFOX 4 cycles > CRT +/– pembrolizumab	pCR: 31.9% (pembrolizumab arm) pCR: 29.4% (control arm)
NICHE (NCT03026140)	Single arm phase II	35	Nivolumab + ipilimumab +/– celecoxib > surgery	pCR: 60% (MSI-H) pPR: 27% (MSS)
NICHE 2 (EudraCT 016-002940-17)	Single arm phase II	112	Nivolumab + ipilimumab > surgery	MPR: 95% pCR: 67%
PICC (NCT03926338)	Non-comparative randomized phase II study	34	Toripalimab ± celecoxib > surgery toripalimab (6 months perioperative treatment)	pCR: 88% (toripalimab+celecoxib) pCR: 65% (toripalimab)

Continued

Table 1 Continued

Trial number	Phase	Sample size	Treatments	Outcomes
NICOLE (NCT04123925)	Single arm phase II	22	Nivolumab 2 cycles > surgery	MPR: 15.8% (MSS) MPR: 0% (MSI-H)
Pei *et al*	Case series	11	ICIs > surgery	MPR: 100% PCR: 90.9%

cCR, clinical complete response; CR, complete response; CRT, chemoradiotherapy; ICIs, immune check-point inhibitors; ITT, intention-to-treat; MPR, major pathological response; MSI-H, microsatellite instability-high; MSS, microsatellite stable tumors; ORR, overall response rate; pCR, pathological complete response; PD, progressive disease; SCRT, short-course radiotherapy; W&W, watch and wait.

Colon cancer

Over the last two decades, conventional treatment of localized CC has been represented by radical surgery followed by 6 months of adjuvant oxaliplatin-based CT for patients with stage III.[43] In this clinical scenario, the use of neoadjuvant chemotherapy (NAC) in resectable localized CC has been investigated in the FOxTROT study.[44] Patients with T3/T4 (N0-2) CC were randomly assigned to receive 6 weeks of NAC (plus panitumumab in the Rat Sarcoma Virus (RAS) wild type (wt) subgroup) followed by surgery and adjuvant CT or the standard approach. Despite initial negative results, in the final analysis the study demonstrated an improvement in 2-year recurrence rate, with significant tumor downstaging and histologic regression after NAC.

dMMR/MSI-H colon cancer

According to the FOxTROT study, low activity was observed in the MSI-H subgroup of patients, with only 7% of RR after NAC. The NICHE trial was the first exploratory study that investigated ICIs as NAT in early-stage CC.[45] Patients with MSI-H and MSS CC received one administration of ipilimumab and two of nivolumab before surgery. Remarkably, at histological examination a pathological response was observed in the 100% of the 20 dMMR cancers, with 60% pCR. By contrast in the MSS population, only 4 out of 15 patients (27%) exhibited pathological responses, with three near complete and one pathologic PR. Subsequently, at the 2022 ESMO annual meeting, the results of the NICHE II study were presented.[46] A total of 112 patients with dMMR localized CC were treated with a short immunotherapy induction consisting, as in the NICHE 1, of one administration of ipilimumab and two of nivolumab followed by surgery within 6 weeks. Pathological response was observed in 106/107 (99%) patients, with 67% of pCR, 95% of MPR and no disease recurrence after a median follow-up of 13.1 months.

In the PICC trial, 34 patients with MSI-H LA CRC were randomly assigned to receive the anti PD-1 toripalimab (with or without celecoxib) followed by surgery and adjuvant therapy.[47] Outstandingly, 15 of 17 patients (88%) in the toripalimab plus celecoxib group and 11 of 17 patients (65%) in the toripalimab monotherapy group showed pCR.

pMMR/MSS colon cancer

Limited evidence is available for ICIs as NAT in MSS CC. In the NICOLE trial, 19 patients with MSS CC (plus 3 MSI-H) received two cycles of nivolumab followed by surgery.[48] MPRs were observed in three pMMR tumors, including one CR. Translational analysis showed a significant increase in lymphocytes infiltration on surgical samples compared with a baseline tumor biopsy. Recently, the promising activity of the combination of NAT with the next generation of ICIs botensilimab plus balstilimab has been reported in patients with MSS CC.[49]

Neoadjuvant ICIs in radically resectable locally advanced upper-GI cancers

Esophageal and gastric cancer

Less than 40% of patients with EGC are diagnosed at an early stage and could be potentially cured by surgery. However, the cure rate by means of surgery alone remains limited and perioperative treatments have been implemented. Currently, the standard of care in western countries relies on the use of FLOT regimen (fluorouracil + leucovorin + oxaliplatin + docetaxel) which improved OS compared with ECF/ECX regimens (epirubicin, cisplatin and 5-fluorouracil/capecitabine).[8] Another option is represented by CRT. The CROSS trial reported a clear benefit in OS for patients treated with preoperative CRT (concomitant CRT with carboplatin and paclitaxel) compared with surgery alone, with median OS 49.4 versus 24 months and 5 years OS 47% versus 34%, respectively.[9] According to preclinical data, NAT with ICIs seems to increase the number of tumor-specific lymphocytes compared with adjuvant therapy, due to the presence of the primary tumor. Moreover, the concurrent administration of CT and/or RT seems to carry an immunomodulatory effect, inducing upregulation of PD-L1 in the tumor microenvironment.[19 50] However, it is important to notice that, since EGC did not show a strong immunogenic signature, ICIs have been tested in combination associated with a perioperative standard of care and this poses questions regarding the best treatment companion for ICIs and the most proper timing of introduction (table 3).

dMMR/MSI-H EGC

The remarkable sensitivity to ICIs in MSI-H cancers encouraged clinicians to assess their efficacy also in

Table 2 Principal ongoing studies of neoadjuvant immunotherapy in localized colorectal cancer

Trial number	Phase	Sample size	Treatment	Outcome (primary endpoint)
PEMREC (NCT04109755)	Single arm phase II study	25	SCRT + pembrolizumab (4 cycles) > surgery	pCR
TARZAN (NCT04017455)	Single arm phase II study	38	SCRT > atezolizumab + bevacizumab > surgery	cCR
NCT04443543	Non-comparative randomized phase II study	222	CRT (FOLFIRINOX OR XELIRI) > surgery/W&W (MSS) Or CRT (FOLFIRINOX OR XELIRI) > tislelizumab > surgery/W&W	cCR
NCT05731726	Single arm phase II study	50	CAPEOX + serpililumab > surgery	pCR
NCT03921684	Single arm phase II study	29	CRT > FOLFOX + nivolumab > surgery	pCR TRAEs
N-PRC (NCT05576480)	Single arm phase II study	55	SCRT + penpulimab > penpulimab + CAPOC (4 cycles) > surgery	pCR
NCT05752136	Randomized phase II study	102	SCRT > CAPOX > surgery Or SCRT > CAPOX + envafolimab > surgery	pCR
(OPTICAL-2) NCT05571644	Randomized phase II study	82	FOLFOXIRI + cadonilimab > surgery Or FOLFOX > surgery	pCR
NCT04621370	Non-comparative randomized phase II study	48	Durvalumab > SCRT > FOLFOX + durvalumab > surgery Or Durvalumab + CRT > FOLFOX + durvalumab > surgery	pCR/cCR
BASKET (NCT04643041)	Single arm phase II study	47	Anti PD-1 (6 cycles) > W&W	1-year DFS rate
NCT04663763	Single arm phase II study	40	SCRT > CAPOX + sintilimab > surgery	pCR
NCT05215379	Phase II randomized study	180	CRT Or CRT+xintilimab > xintilimab (up to 4 cycles)	cCR
NCT05507112	Single arm phase II study	100	Tislelizumab + CRT	pCR
NCT04357587	Single arm phase II study	10	Pembrolizumab + CRT >surgery	TRG Safety
TORCH (NCT04518280)	Randomized non-comparative phase II study	130	SCRT > CAPOX + camrelizumab 6 cycles > surgery/W&W Or CAPOX + camrelizumab 2 cycles > SCRT > CAPOX + camrelizumab 4 cycles > surgery/W&W	CR
PICC (NCT03926338)	Non-comparative randomized phase II study	69	Toripalimab ± celecoxib > surgery toripalimab (6 months perioperative treatment)	pCR
NAIO (NCT05239546)	Single arm phase II study	25	Dostarlimab 12 cycles	MCR
NCT04625803	Single arm phase II study	64	FOLFOX + camrelizumab 6 cycles > apatinib 2 months > surgery	TRG
NCT05662527	Single arm phase II study	85	Pembrolizumab 1 cycle > surgery	pCR

Continued

Table 2 Continued

Trial number	Phase	Sample size	Treatment	Outcome (primary endpoint)
NCT04231526	Non-comparative randomized phase II study	46	Pembrolizumab 2 cycles > surgery Or Surgery	Feasibility of neoadjuvant treatment
NCT05202314	Single arm phase II study	20	Camrelizumab+ FOLFOX (3 cycles)/CAPOX (2 cycles) > surgery	pCR

. cCR, clinical complete response; CRT, chemoradiotherapy; DFS, disease-free survival; MCR, major clinical response; MSI-H, microsatellite instability; MSS, microsatellite stable tumors; NR, not reported; pCR, pathological complete response; PD-1, programmed cell death 1 ; SCRT, short course radiotherapy; TRAE, treatment-related adverse events; TRG, tumor regression grade; TRG, tumor regression grade; W&W, watch and wait.

earlier settings of EGC. A subgroup analysis from the DANTE trial, showed that MSI-H cancers were more likely to achieve a pCR, with 46% compared with 24% of MSS cancers.[51] Moreover, among MSI-H cancers those treated with FLOT + atezolizumab achieved complete or subtotal regression in 80% of cases, compared with 59% of those treated with FLOT alone. It has been reported that MSI status could negatively impact responsiveness to CT, particularly to fluoropyrimidines, as shown in the previous meta-analysis.[52] Thus, investigating whether perioperative CT, and the related toxicity, can be avoided if replaced with ICIs has gained high clinical interest. Two phase II trials investigated this topic. The former, the GERCOR NEONIPIGA trial, enrolled patients with radically resectable EGC who underwent preoperative immunotherapy with nivolumab plus ipilimumab and adjuvant nivolumab.[53] The primary endpoint was the pCR rate, with a threshold of 20% considered acceptable. Results showed a pCR rate of 58.6%, therefore meeting the primary endpoint. Of note three patients did not undergo surgery, one due to inclusion deviation as it was metastatic at diagnosis and two due to patient refusal. All three cases achieved CR as per radiological, endoscopic, and histologic assessment. The latter one, the INFINITY trial, is an ongoing phase II study of durvalumab + tremelimumab in radically resectable MSI-H EGC.[54] The therapy is administered either as NAT (cohort 1) or as definitive treatment (cohort 2). Preliminary results from cohort 1 have recently been published and reported a pCR rate of 60% and an MPR rate of 80%. All patients who achieved pCR had negative circulating tumor DNA before surgery and none of the patients who received surgery experienced disease relapse at the time of this analysis. These results spurred the investigators to move forward to assess the non-operative approach in cohort 2, which is currently recruiting patients.

Eventually, the IMHOTEP trial is an ongoing phase II trial of MSI-H solid cancers, which aims to assess whether a limited number of cycles (one or two cycles) of pembrolizumab administered preoperatively may be sufficient to reach a higher pCR rate, compared with historical control.[55] After the first preliminary analysis, a pCR rate of 38.9% in the overall population (colorectal, gastroesophageal, endometrial, and other cancers) has been reported, with a 25% rate in the gastroesophageal cohort. These data were lower than those previously reported, but it should be noticed that a high percentage of patients did not undergo surgery due to their own choice after reaching a cCR, potentially impacting the rate of pCR.

pMMR/MSS EGC

Several trials tested the combination of ICIs with the standard of care in the setting of biomarker unselected EGC. The addition of atezolizumab to FLOT in the DANTE trial was safe in terms of surgical morbidity and mortality and demonstrated an improvement in main pathological outcomes at an interim analysis. The clinical PR rate was higher in the atezolizumab group, both in the overall population (tumor regression grade (TRG) 1a 24% vs 15%) and in cancers with high PD-L1 (combined positive score (CPS) ≥10) (TRG1a 38% vs 14%). Accordingly, macroscopical downsizing favored atezolizumab addition compared with CT alone (pT0 23% vs 15%).[56] Data regarding primary endpoint progression-free survival (PFS) are not yet available and will define whether pathological outcomes translate into improved clinical outcomes. Currently, two randomized phase III clinical trials (KEYNOTE-585 and MATTERHORN) are investigating the addition of anti-PD-1/PD-L1, pembrolizumab and durvalumab, respectively, to perioperative CT in gastric or junctional adenocarcinoma, respectively.[57 58] Preliminary results of a prespecified analysis from the KEYNOTE-585 trial have recently been released. pCR rate, one of the primary endpoints was significantly increased with the addition of pembrolizumab, whereas event-free survival (EFS) did not show a statistically significant improvement and, therefore, median OS was not tested. Similarly, an interim analysis has recently shown the addition of durvalumab to preoperative FLOT regimen to improve pCR rate, a secondary endpoint. Data regarding the primary endpoint EFS, and the other secondary endpoint OS are still awaited. Recently, an Asian study reported preliminary outcomes of NAC plus

Table 3 Completed and ongoing trial of neoadjuvant immunotherapy in esophageal and gastric cancer

Histology	Trial number	Ph	Treatment	Sample size	Outcome (pCR rate)	Status
ESCC	NCT05357846	3	Tislelizumab/aclitaxel/cisplatin/radiation	422	NR	Ongoing
ESCC	NCT05043688	2	Camrelizumab/albumin paclitaxel/carboplatin/radiation	204	NR	Not yet recruiting
ESCC	NCT04974047	2	Tislelizumab/paclitaxel/cisplatin/radiation	70	NR	Ongoing
ESCC	NCT04973306	2/3	Tislelizumab/paclitaxel/carboplatin/radiation	176	NR	Ongoing
ESCC	NCT04776590	2	Tislelizumab/albumin paclitaxel/caboplatin/radiation	30	46.7%	Ongoing
ESCC	NCT04644250	2	Toripalimab/paclitaxel liposome/carboplatin/radiation	32	NR	Ongoing
ESCC	NCT04568200	2	Durvalumab/paclitaxel/carboplatin/radiation	60	NR	Ongoing
ESCC	NCT04435197	2	Pembrolizumab/carboplatin/paclitaxel/radiation	143	NR	Ongoing
EGJAC	NCT03544736	1/2	Nivolumab/paclitaxel/carboplatin/radiation	30	NR	Ongoing
EGJAC	NCT03064490	2	Pembrolizumab/paclitaxel/carboplatin/radiation	38	35.7%	Completed
ESCC	NCT04006041	2	Toripalimab/paclitaxel/cisplatin/radiation	44	50%	Completed
ESCC	NCT05244798	3	Sintilimab/albumin paclitaxel/carboplatin±radiation	420	NR	Not yet recruiting
ESCC	NCT05355168	1/2	Camrelizumab/nimotuzumab/carboplatin/paclitaxel/radiation	57	NR	Ongoing
GAC/ EGJAC	NCT03776487	1/2	Ipilimumab/nivolumab/5-fluorouracil/oxaliplatin/radiation	36	NR	Ongoing
EAC/ EGJAC	NCT03087864	2	Atezolizumab/carboplatin/paclitaxel/radiation	40	30.3%	Completed
EAC/ EGJAC	NCT02962063	1/2	Durvalumab/tremelimumab/carboplatin/paclitaxel/radiation (induction FOLFOX 2 cycles)	78	22.2%	Ongoing
			Durvalumab/tremelimumab/5-fluorouracil or capecitabine/ oxaliplatin/radiation (induction FOLFOX 2 cycles)		NR	
ESCC	NCT05476380	2	Camrelizumab/paclitaxel/cisplatin	39	17.6%	Completed
ESCC	NCT05302011	2	Pembrolizumab/docetaxel/carboplatin or cisplatin	30	NR	Ongoing
ESCC	NCT05281003	2	Pembrolizumab/paclitaxel/cisplatin	128	NR	Ongoing
ESCC	NCT05213312	2/3	Nivolumab/paclitaxel or 5-fluorouracil/cisplatin	90	NR	Ongoing
ESCC	NCT05189730	2	Tislelizumab/paclitaxel/cisplatin	80	NR	Ongoing
ESCC	NCT05182944	2	Camrelizumab/albumin paclitaxel/cisplatin	130	35.8%	Ongoing
ESCC	NCT05174325	2	Sintilimab/albumin paclitaxel/cisplatin	30	NR	Ongoing
ESCC	NCT05050760	NA	Camrelizumab/oxaliplatin/docetaxel/tegafur	55	NR	Ongoing
ESCC	NCT04848753	3	Toripalimab/paclitaxel/cisplatin	663	NR	Ongoing
EGJAC	NCT04813523	2	Pembrolizumab/5-fluorouracil/cisplatin	30	NR	Ongoing
ESCC	NCT04807673	3	Pembrolizumab/paclitaxel/cisplatin	342	NR	Ongoing
ESCC	NCT04804696	2	Toripalimab/paclitaxel/cisplatin	53	NR	Ongoing

Continued

Table 3 Continued

Histology	Trial number	Ph	Treatment	Sample size	Outcome (pCR rate)	Status
ESCC	NCT04506138	2	Camrelizumab/albumin paclitaxel/carboplatin	46	21.6%	Completed
ESCC	NCT04460066	1b/2	Socazolimab or placebo/albumin paclitaxel/cisplatin	70	41.4 vs 27.6%	Completed
ESCC	NCT04389177	2	Pembrolizumab/carboplatin/paclitaxel	50	41.4%	Ongoing
ESCC	NCT04280822	3	Toripalimab or placebo/paclitaxel/cisplatin	400	15.7 vs 3.2%	Ongoing
GAC/ EGJAC	NCT04221555	2	Durvalumab/docetaxel/oxaliplatin/S-1	68	29%	Ongoing
ESCC	NCT03946969	1/2	Sintilimab/liposomal paclitaxel/cisplatin/S-1	30	20%	Completed
ESCC	NCT03917966	2	Camrelizumab/docetaxel/nedaplatin	40	39.6%	Completed
EGJAC	NCT04757363	2	Nivolumab/regorafenib/oxaliplatin/5-fluorouracil	35	N.A.	Completed
ESCC	NCT04666090	2	Carrelizumab/albumin paclitaxel/nedaplatin/apatinib	42	NR	Ongoing
ESCC	ChiCTR2100045659	2	Sintilimab/albumin paclitaxel/cisplatin	30	17%	Completed
ESCC	NCT03985670	2	Toripalimab/paclitaxel/cisplatin	30	20.8%	Completed
ESCC	ChiCTR1900026240	2	Camrelizumab/albumin paclitaxel/carboplatin	60	39.2%	Completed
ESCC	NCT04225364	2	Camrelizumab/albumin paclitaxel/cisplatin	56	31.4%	Completed
ESCC	ChiCTR2000037488	2	Tislelizumab/albumin paclitaxel/carboplatin	45	50%	Completed
EAC/GAC/ EGJAC	NCT03399071	2	Avelumab/5-fluorouracil/oxaliplatin/docetaxel	44	15% (prematurely closed)	Completed
EAC/ EGJAC	NCT03604991	2/3	Nivolumab or nivolumab/CROSS or CROSS or nivolumab/ ipilimumab	278	NR	Ongoing
EAC/ EGJAC	NCT03784326	1	Atezolizumab/5-fluorouracil/oxaliplatin	40	11%	Ongoing
GAC/EGJAC	NCT02918162	2	Pembrolizumab/capecitabine or 5-fluorouracil/oxaliplatin/ (optional epirubicin)	40	20.6%	Completed

.EAC, esophageal adenocarcinoma; EGJAC, esophago-gastric junction adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GAC, gastric adenocarcinoma; NA, not available; NR, not reported; pCR, pathologic complete response; ph, phase.

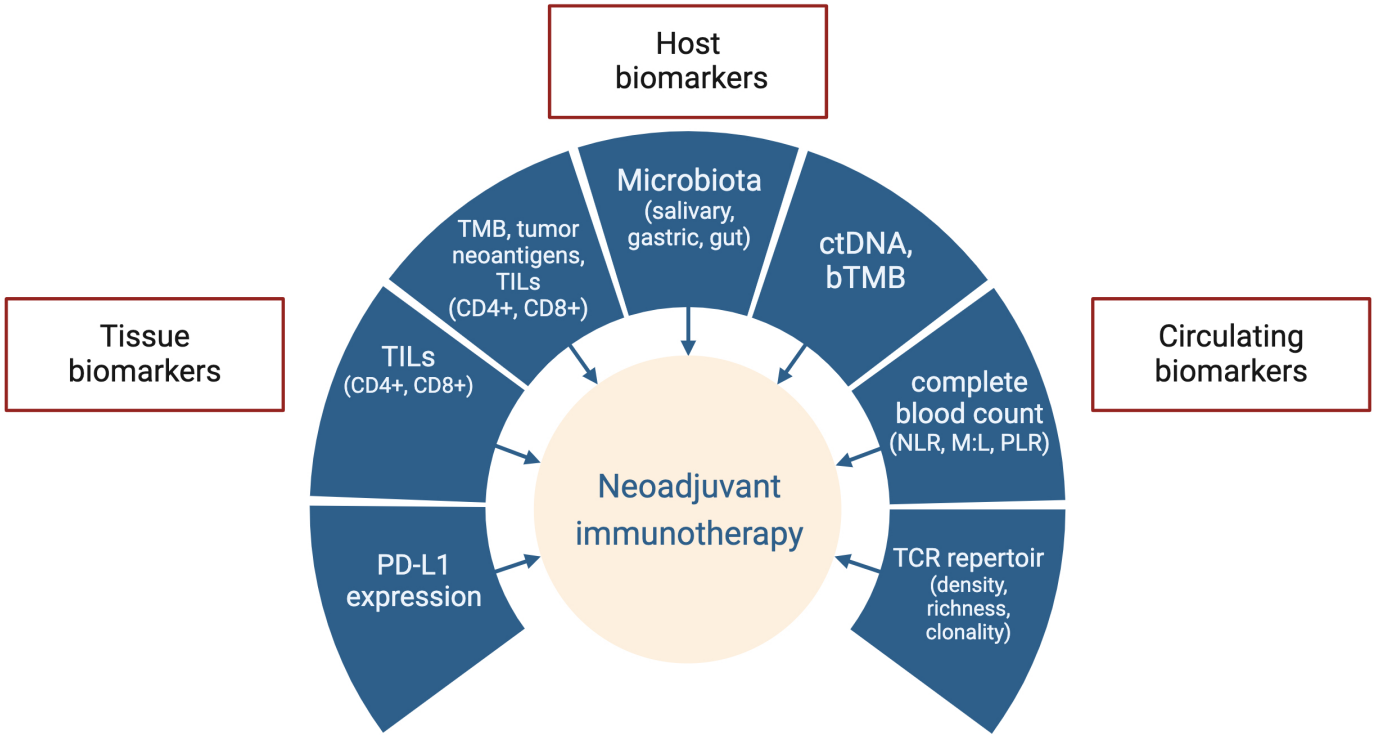

Figure 3 Biomarkers under investigation for neoadjuvant immune checkpoint inhibitors in gastrointestinal cancers. bTMB, blood-based tumor mutation burden; ctDNA, circulating tumor DNA; M:L, myeloid to lymphoid ratio; MSI, microsatellite instability; MMR, mismatch repair; NLR, neutrophil to lymphocyte ratio; PD-L1, programmed cell death-ligand 1; PLR, platelet to lymphocyte ratio; TCR, T-cell receptor; TILs, tumor infiltrating lymphocytes; TMB, tumor mutation burden.

camrelizumab versus NAC alone in ESCC.[59] Co-primary endpoints were pCR rate and 5 years OS rate. Data for pathological outcomes showed an increase in pCR and MPR rates by the addition of camrelizumab to CT (27.8% vs 10% and 43.3% vs 26.7%, respectively), but survival outcomes and relationship to PD-L1 expression are not yet available. Likewise, the ongoing HCHTOG1909 clinical trial is investigating the role of toripalimab added to neoadjuvant CT versus CT alone in ESCC.[60] The interim analysis reported around five times the pCR rate with the addition of toripalimab to CT (15.7% vs 3.2%). Considering the promising results reported in phase II and III trials, questions about the best modality to associate ICIs are rising. A Chinese trial has addressed this topic by randomizing patients to receive either two or four cycles of camrelizumab in association with NAC in ESCC. Results showed superiority in terms of RR and pCR rate for the four cycles group without a significantly higher rate of toxicities.[61] Moving to CRT, few studies are currently assessing the addition of ICIs in EGC. The KEYNOTE-975 is an ongoing phase III trial that randomized patients with LA EGC to receive pembrolizumab plus definitive CRT versus definitive CRT alone.[62] The phase II/III trial ECOG-ACRIN-2174 is ongoing and is investigating pCR rate and DFS of EGC treated with preoperative CRT according to CROSS regimen with or without concomitant nivolumab.[63] After surgery, patients will be further randomized to adjuvant nivolumab with or without ipilimumab. So far, only toxicity data are available and the addition of nivolumab to CRT did not significantly increase the rate of side effects, without any new safety concerns.

CONCLUSIONS

Over the last years, ICIs have been introduced into the clinical practice in metastatic EGC and CRC and, recently, new insights were reported in early-stage disease. NAT is a standard treatment for radically resectable LA EGC and RC, and it provides an optimal setting for ICIs administration, due to wide neo-antigens, low tumor clonalities and a naïve immune system.[64] However, besides the solid biological rationale, ICIs use is far from being set as the standard of care for NAT in unselected populations.

Due to considerable differences in biology and responses to treatments, in this review, we differentiated MSS from MSI-H cancers.[65] Results obtained in the MSI-H-specific subgroup have been changing the treatment scenario of GI cancers, sparing CT, RT and even surgery, with a significant benefit in survival[32 53 66] The current data are changing the clinical approach to manage patients with LA radically resectable EGC and RC, even though they are still immature to support a drastic change of clinical practice.

However, it is probably only a matter of time. If larger randomized clinical trials with a longer follow-up should confirm some initial impressive results in the MSI-H population, in LA EGC and RC we will assist in a de-escalation

revolution. Nevertheless, it should be noted that even a proportion of MSI-H cancers did not benefit from ICIs treatment, and it needs to be rapidly investigated into details. Several biomarkers, both circulating and tissual, have been tested for their prognostic or predictive value in EGC, but results are not yet conclusive[67] (figure 3). Moreover, some molecular features seem to negatively impact outcomes of MSI-H EGC as well as responses to PD-1 blockade and require further evaluations.[68 69] Therefore, the implementation of molecular profiling could help to assess the real impact of concomitant mutations in MSI-H GI cancers.

Unfortunately, most GI cancers do not display a highly immunogenic profile, conversely to melanoma or lung cancer.[70] Hence, the success of ICIs use as NAT in biomarker unselected patients remains far from being achieved.

In LARC, even though signals of synergistic clinical activity were observed, combining ICIs with multimodal NAT in MSS tumors produced fewer strickling results than those in the MSI-H subset. However, there are different crucial points to consider. First, it is still unknown what is the best NAT (SCRT followed by chemo-immunotherapy/immunotherapy vs CRT plus immunotherapy). Second, the identification of predictive biomarkers of response is required for improving patients' selection and treatment efficacy. Third, randomized studies are needed to demonstrate the potential room for ICIs as a part of NAT in MSS LARC. Similar questions are present in LA EGC, another field where NAT is the current standard of care. The addition of ICIs to CT did not translate into a meaningful clinical benefit, as reported in the pivotal phase III KEYNOTE-585 trial. Several methodological and statistical considerations could be done to interpret those results, but at the bottom there is the failure of the "one size fits all" strategy. A reliable and precise stratification of patients according to clinical, pathologic, and molecular biomarkers is urgently required, to give the best personalized therapeutic option to any single patient. Additionally, further synergistic combinations could be worthwhile in this setting. Other signaling processes such as tumor angiogenesis play crucial a role in cancer progression and may be tackled by approved drugs,[71] even though their role in NAT is not yet clinical practice. According to recent reports, the addition of the antiangiogenic agent apatinib to CT and ICIs improved pCR rate in a single-arm phase II trial of LAEGC.[72] In conclusion, the addition of ICIs to NAT in GI cancers represents a thorny field for research since despite promising results, its widespread use was not associated with a global significant clinical benefit. Further strategies should be designed, rethinking the approach and trying to overcome the intrinsic low immunogenic profile of GI cancers.

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