dMMR/MSI-High Gastrointestinal Cancers

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Immune checkpoint inhibitors have revolutionized the management of mismatch repair-deficient (MMR-D)/microsatellite instability-high (MSI-H) gastrointestinal cancers, particularly colorectal cancer. Cancers with the MMR-D/MSI-H genotype often carry a higher tumor mutation burden with frameshift alterations, leading to increased mutation-associated neoantigen (MANA) generation. The dramatic response seen with immune checkpoint inhibitors (ICIs), which are orchestrated by MANA-primed effector T cells, resulted in the rapid development of these novel therapeutics within the landscape of MSI-H gastrointestinal cancers.

immunotherapy neoadjuvant therapy gastrointestinal cancers

1. Neoadjuvant Immunotherapy for Patients with dMMR/MSI-H Rectal Cancer

The standard therapies for locally advanced rectal cancer remain surgery, chemoradiation, and systemic chemotherapy. The current literature supports that dMMR/MSI-H rectal cancer is inherently resistant to fluoropyrimidine, leading to unfavorable survival outcomes [1][2][3][4]. Notably, surgical resection and/or radiotherapy carries a significant risk for ostomy creation, fecal incontinence, and/or urinary and sexual dysfunction [5][6][7]. Therefore, over the last few decades, investigators have focused on a total neoadjuvant approach in locally advanced rectal cancer treatment to provide organ preservation and improve long-term prognosis [8][9][10][11]. Early studies with total neoadjuvant trials showed that patients with rectal cancer harboring MMR-D undergoing induction chemotherapy might experience disease progression, while this was not noted for patients with MSS disease [2]. Therefore, it has become evident that a total neoadjuvant approach with induction chemotherapy may not be the ideal therapeutic approach for patients with MMR-D/MSI-H rectal cancer.

ICI therapies have been approved for patients with metastatic dMMR/MSI-H CRC as first-line therapies with durable responses [12]. Fluoropyrimidine resistance seen with MSI-H biology and the breakthrough efficacy of ICI therapy in the metastatic setting led to many clinical trials to evaluate the neoadjuvant role of these agents for patients with locally advanced dMMR/MSI-H rectal cancer. Cercek et al. conducted a single-institution phase II trial with dostarlimab monotherapy, an anti-PD1 monoclonal antibody, in locally advanced stage II or III dMMR/MSI-H rectal cancer [13].

The sequential use of ICIs with chemoradiation was also investigated in several studies. Bando et al. investigated neoadjuvant nivolumab plus chemoradiotherapy in patients with locally advanced dMMR/MSI-H and pMMR/MSS

rectal cancer [14]. Three of five dMMR/MSI-H rectal cancer patients achieved pathologic CR (60%). Perhaps it is important to note that radiation may directly affect the effectiveness of tumor-infiltrating lymphocytes, which are key immune cells to mediate ICI response. A phase II VOLTAGE-A trial evaluated the use of five cycles of nivolumab after chemoradiation in locally advanced dMMR/MSI-H and pMMR/MSS rectal cancer [15]. At the time of the preliminary results of this trial, 5 patients with MSI-H rectal cancer were enrolled, and pathologic CR was noted to be 60% (3/5). None of the patients with MSI-H rectal cancer had recurrent disease. Currently, the ECOG-ACRIN phase II trial (EA2201) is actively investigating whether neoadjuvant nivolumab plus ipilimumab and short-course radiation in locally advanced dMMR/MSI-H rectal cancer would result in increased pCR rates (NCT04751370). However, this study has been modified due to the highly promising outcomes of dostarlimab monotherapy, and patients will undergo interim evaluation following immunotherapy induction therapy, and patients who achieve complete clinical response will undergo a watch-and-wait approach without a short course of radiation. Another phase I study investigating pembrolizumab in combination with conventional chemoradiation with capecitabine is actively recruiting (NCT04357587). The accumulating evidence suggests a majority of patients with MSI-H rectal cancer may not need chemoradiation, and long-term adverse complications of pelvic radiation should be considered when investigating ICI therapy in this setting.

2. Neoadjuvant Immunotherapy for Patients with dMMR/MSI-H Colon Cancer

Similar to rectal cancer, studies have investigated the role of immune checkpoint inhibitor therapy as neoadjuvant therapy for patients with MSI-H colon cancer. The NICHE study pioneered the use of neoadjuvant ICI therapy for stage I (10%), II (10%), and III (80%) dMMR/MSI-H colon cancer [16]. The study investigated neoadjuvant nivolumab (anti-PD-1 antibody) plus ipilimumab (anti-CTLA-4 antibody) in resectable colon cancer patients with either dMMR/MSI-H or pMMR/MSS. Patients received two doses of 3 mg/kg nivolumab and a single dose of 1 mg/kg ipilimumab. All patients with dMMR/MSI-H colon cancer (32/32) achieved a pathologic response, and among those, 97% (31/32) of them had a major pathologic response (less than 10% viable tumor), and 22/32 (69%) of them achieved complete pathologic response after a median follow-up time of 25 months. The nivolumab plus ipilimumab combination was safe, feasible, and well tolerated. Subsequently, the NICHE-2 study evaluated the nivolumab plus ipilimumab combination in a larger cohort of 107 nonmetastatic dMMR/MSI-H colon cancer patients [17]. A major pathologic response was observed in 102 patients (95%); among those, 72 patients had pathological CR (67%), indicating a deep pathological response with neoadjuvant immunotherapy. At a median follow-up of 13 months, none of the patients had disease recurrence. Immune-related severe adverse events (grade 3 or 4) were seen in only three patients (3%). The PICC study, a phase II trial, is currently investigating neoadjuvant toripalimab (anti-PD1 monoclonal antibody) with or without celecoxib in 34 patients with locally advanced dMMR/MSI-H colon cancer [18]. The patients were treated for up to 6 months, followed by surgery. Early results showed that pathologic CR rates were 88% and 65% with the toripalimab plus celecoxib and toripalimab-only groups, respectively. At a median follow-up of 14.9 months, all patients were alive and disease-free, consistent with a highly effective approach with neoadjuvant immunotherapy.

Zhou et al. published a meta-analysis of neoadjuvant immunotherapy for nonmetastatic CRC. Among 113 cases with nonmetastatic dMMR/MSI-H CRC, the pathologic CR and major pathologic response were 63.9% and 80.3%, respectively [19]. Another phase II study is currently evaluating neoadjuvant tislelizumab (anti-PD1 antibody) in locally advanced dMMR/MSI-H CRC (NCT05116085). Early results reported that all patients (18/18, 100%) achieved significant regression. Five patients with locally advanced dMMR/MSI-H colon cancer had confirmed pathologic CR after surgery [20]. The NEOPRISM-CRC trial is also currently investigating pembrolizumab in patients with dMMR/MSI-H CRC or high TMB (≥20 mutations per megabase) [21].

Although promising clinical effects of neoadjuvant immunotherapy in locally advanced dMMR/MSI-H CRC have been reported, there are no controlled clinical trials to compare adjuvant ICI therapy with the neoadjuvant approach [22][23]. In the ATOMIC trial, patients with MSI-H stage III colon cancer were randomized into chemotherapy vs. chemoimmunotherapy with atezolizumab and FOLFOX to evaluate the additive role of immune checkpoint therapy in the adjuvant setting. However, atezolizumab was not investigated as a monotherapy in this study, and whether these patients even need chemotherapy will not be answered in this clinical trial. More studies comparing neoadjuvant and adjuvant immune checkpoint inhibitor therapies should be investigated to better define the role of neoadjuvant immunotherapy for locally advanced colon cancer.

3. Neoadjuvant Immunotherapy for Patients with dMMR/MSI-H CRC and Distant Metastasis

The effectiveness of ICI therapy for advanced-stage CRC has been well established; however, little is known about the depth of pathologic response for those undergoing metastasectomy or cytoreductive surgery. Jin and colleagues conducted a retrospective controlled study with 75 dMMR/MSI-H metastatic CRC patients [24]. Among them, 16 patients had metastasectomy of liver lesions. Six patients received adjuvant pembrolizumab. The median overall survival (OS) was significantly higher among the dMMR/MSI-H metastasectomy group compared with those who did not undergo metastasectomy (82 mo vs. 13.9 mo, retrospectively). Also, it was evident that patients with dMMR/MSI-H metastatic CRC had a greater benefit from metastasectomy compared with the pMMR/MSS group (median OS: 82 mo vs. 69.9 mo, retrospectively). However, this study did not include patients with neoadjuvant ICI therapy; therefore, the role of ICI therapy remains unclear for patients with resectable liver metastasis yet should be considered, given the deep and durable responses seen with ICIs. Whether pathological response impacts the long-term outcomes and whether metastasectomy is even needed in this population warrant future studies. Notably, several case series and reports of CRC patients with MSI-H CRC with peritoneal metastasis have shown promising results with ICI therapy. In a case series of patients with MSI-H CRC with peritoneal carcinomatosis, eight patients underwent cytoreductive surgery after induction ICI therapy, and notably, seven out of eight patients (87%) achieved complete pathological response [25]. This dramatic pathologic response was also noted in other case reports. Tonello et al. reported a patient with Lynch Syndrome who was treated with nivolumab 240 mg every two weeks. After two years of stable disease with ICI therapy, the patient underwent cytoreductive surgery (CRS), which showed a complete pathologic response [26]. After nine months of follow-up, no disease recurrence was noted. In another case report, the authors discussed the case of a 46-year-old patient with MSI-H CRC with

peritoneal carcinomatosis without a history of Lynch presented who was treated with pembrolizumab monotherapy. The patient achieved a complete pathological response confirmed via tissue samples obtained during the cytoreductive surgery [27]. These results, although limited, indicate that deep pathological responses can be seen among patients with MSI-H CRC and peritoneal carcinomatosis. Further large-scale studies are needed for tailoring surgical strategies, including colorectal resection, metastasectomy, debulking, HIPEC, and/or the watch-and-wait approach for patients with dMMR/MSI-H metastatic CRC in the immunotherapy era.

4. Neoadjuvant Immunotherapy for Patients with dMMR/MSI-H Gastric and Esophagogastric Junction Cancers

Over the past few decades, research has been directed towards integrating systemic treatments for locally advanced gastric and GEJ cancers to achieve better survival outcomes and increase the R0 surgical resection rates [28][29][30][31]. The current standard of care for patients with locally advanced gastric cancer consists of neoadjuvant chemotherapy or surgical resection followed by adjuvant chemotherapy [28][32][33]. The MAGIC trial showed a 79% R0 resection rate for neoadjuvant chemotherapy in locally advanced gastric and GEJ cancers [28]. Despite this, the pathologic response association with OS was suboptimal, with approximately 10% pathologic CR. A meta-analysis of four randomized clinical trials evaluated the prognostic value of MSI in gastric cancer patients [34]. The authors reported that dMMR/MSI-H was associated with better OS and disease-free survival (DFS) at five years. However, patients with gastric cancer with dMMR/MSI-H had worse outcomes when treated with perioperative chemotherapy [35]. Furthermore, neoadjuvant chemotherapy led to an increased incidence of complications related to surgery [36].

The dMMR/MSI-H phenotype is seen in approximately 5–10% of gastric and GEJ cancers [34][37][38]. As noted in several studies, dMMR/MSI-H is associated with a decreased benefit from fluoropyrimidine-based chemotherapy with respect to OS and DFS [34][39]. In Checkmate 649, MSI-H was the most important predictor of response to chemoimmunotherapy, consistent with the observations seen among patients with MSI-H CRC [40]. Due to these facts, studies have investigated ICI therapy as a neoadjuvant treatment. In a randomized, open-label, phase II trial (DANTE), Al-Batran et al. reported improved pathologic CR by adding atezolizumab to neoadjuvant platinum and fluoropyrimidine-based chemotherapy in patients with resectable GEJ cancer, particularly those with MSI-H disease [41]. In the phase II NEONIPIGA trial, Andre et al. evaluated a neoadjuvant nivolumab plus ipilimumab combination in locally advanced dMMR/MSI-H gastric or GEJ cancer patients [42]. In the study, 50% (16 patients) had gastric cancer, and the other half had GEJ cancer. Patients received nivolumab 240 mg once every two weeks for six cycles and ipilimumab 1 mg/kg once every six weeks for two cycles, followed by surgery and adjuvant nivolumab 480 mg once every four weeks for nine cycles. Three patients had a complete CR and did not have surgery. All 29 patients who underwent surgery had R0 resection, and 58.6% (17 patients) had pathologic CR. At 12 months of median follow-up, 93.7% (30 patients) were alive without recurrence. The nivolumab plus ipilimumab combination treatment was well tolerated, with grade ≥3 immune-related adverse events of 25%. Currently, a multicenter, phase II INFINITY trial (NCT04817826) is investigating the efficacy and safety of a neoadjuvant tremelimumab plus durvalumab combination in dMMR/MSI-H gastric or GEJ cancer patients [43]. In the first cohort

of this trial, 15 patients were evaluated after a single dose of tremelimumab and three doses of durvalumab once every four weeks, followed by surgery. The pathologic CR was 60% (9/15), and the major complete pathologic response was 80%, indicating that deep pathological response may offer a path for a potential nonoperative approach for patients with MSI-H gastric and GEJ cancers. Grade ≥3 immune-related adverse events were observed in three patients; all responded well to high-dose steroids [44].

In a meta-analysis, Li et al. assessed 21 prospective phase I/II studies comprising 687 patients with locally advanced gastric or GEJ cancer treated with neoadjuvant ICI therapy [45]. They reported that dMMR/MSI-H was associated with improved pathological CR and major pathologic response rates than pMMR/MSS when patients are treated with ICI therapy. Despite their heterogeneity, the results suggest that ICI-based neoadjuvant treatment is safe and feasible and produces superior pathologic responses for patients with the dMMR/MSI-H phenotype.

References

1. Carethers, J.M.; Smith, E.J.; Behling, C.A.; Nguyen, L.; Tajima, A.; Doctolero, R.T.; Cabrera, B.L.; Goel, A.; Arnold, C.A.; Miyai, K.; et al. Use of 5-fluorouracil and survival in patients with microsatellite-unstable colorectal cancer. Gastroenterology 2004, 126, 394–401.
2. Cercek, A.; Dos Santos Fernandes, G.; Roxburgh, C.S.; Ganesh, K.; Ng, S.; Sanchez-Vega, F.; Yaeger, R.; Segal, N.H.; Reidy-Lagunes, D.L.; Varghese, A.M.; et al. Mismatch Repair-Deficient Rectal Cancer and Resistance to Neoadjuvant Chemotherapy. Clin. Cancer Res. 2020, 26, 3271–3279.
3. Sargent, D.J.; Marsoni, S.; Monges, G.; Thibodeau, S.N.; Labianca, R.; Hamilton, S.R.; French, A.J.; Kabat, B.; Foster, N.R.; Torri, V.; et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J. Clin. Oncol. 2010, 28, 3219–3226.
4. Samowitz, W.S.; Curtin, K.; Wolff, R.K.; Tripp, S.R.; Caan, B.J.; Slattery, M.L. Microsatellite instability and survival in rectal cancer. Cancer Causes Control 2009, 20, 1763–1768.
5. Li, K.; He, X.; Tong, S.; Zheng, Y. Risk factors for sexual dysfunction after rectal cancer surgery in 948 consecutive patients: A prospective cohort study. Eur. J. Surg. Oncol. 2021, 47, 2087–2092.
6. Ridolfi, T.J.; Berger, N.; Ludwig, K.A. Low Anterior Resection Syndrome: Current Management and Future Directions. Clin. Colon. Rectal Surg. 2016, 29, 239–245.
7. Peeters, K.C.; van de Velde, C.J.; Leer, J.W.; Martijn, H.; Junggeburt, J.M.; Kranenbarg, E.K.; Steup, W.H.; Wiggers, T.; Rutten, H.J.; Marijnen, C.A. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: Increased bowel dysfunction in irradiated patients—A Dutch colorectal cancer group study. J. Clin. Oncol. 2005, 23, 6199–6206.

8. Xu, Z.; Mohile, S.G.; Tejani, M.A.; Becerra, A.Z.; Probst, C.P.; Aquina, C.T.; Hensley, B.J.; Arsalanizadeh, R.; Noyes, K.; Monson, J.R.; et al. Poor compliance with adjuvant chemotherapy use associated with poorer survival in patients with rectal cancer: An NCDB analysis. Cancer 2017, 123, 52–61.
9. Rahma, O.E.; Yothers, G.; Hong, T.S.; Russell, M.M.; You, Y.N.; Parker, W.; Jacobs, S.A.; Colangelo, L.H.; Lucas, P.C.; Gollub, M.J.; et al. Use of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: Initial Results from the Pembrolizumab Arm of a Phase 2 Randomized Clinical Trial. JAMA Oncol. 2021, 7, 1225–1230.
10. van der Valk, M.J.M.; Marijnen, C.A.M.; van Etten, B.; Dijkstra, E.A.; Hilling, D.E.; Kranenbarg, E.M.; Putter, H.; Roodvoets, A.G.H.; Bahadoer, R.R.; Fokstuen, T.; et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer—Results of the international randomized RAPIDO-trial. Radiother. Oncol. 2020, 147, 75–83.
11. Garcia-Aguilar, J.; Chow, O.S.; Smith, D.D.; Marcet, J.E.; Cataldo, P.A.; Varma, M.G.; Kumar, A.S.; Oommen, S.; Coutsoftides, T.; Hunt, S.R.; et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: A multicentre, phase 2 trial. Lancet Oncol. 2015, 16, 957–966.
12. André, T.; Shiu, K.K.; Kim, T.W.; Jensen, B.V.; Jensen, L.H.; Punt, C.; Smith, D.; Garcia-Carbonero, R.; Benavides, M.; Gibbs, P.; et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N. Engl. J. Med. 2020, 383, 2207–2218.
13. Cercek, A.; Lumish, M.; Sinopoli, J.; Weiss, J.; Shia, J.; Lamendola-Essel, M.; El Dika, I.H.; 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, 2363–2376.
14. Bando, H.; Tsukada, Y.; Inamori, K.; Togashi, Y.; Koyama, S.; Kotani, D.; Fukuoka, S.; Yuki, S.; Komatsu, Y.; Homma, S.; et al. Preoperative Chemoradiotherapy plus Nivolumab before Surgery in Patients with Microsatellite Stable and Microsatellite Instability-High Locally Advanced Rectal Cancer. Clin. Cancer Res. 2022, 28, 1136–1146.
15. Yuki, S.; Bando, H.; Tsukada, Y.; Inamori, K.; Komatsu, Y.; Homma, S.; Uemura, M.; Kato, T.; Kotani, D.; Fukuoka, S.; et al. SO-37 Short-term results of VOLTAGE-A: Nivolumab monotherapy and subsequent radical surgery following preoperative chemoradiotherapy in patients with microsatellite stability and microsatellite instability-high, locally advanced rectal cancer (EPOC 1504). Ann. Oncol. 2020, 31, S230–S231.
16. Chalabi, M.; Fanchi, L.F.; Dijkstra, K.K.; Van den Berg, J.G.; Aalbers, A.G.; Sikorska, K.; Lopez-Yurda, M.; Grootscholten, C.; Beets, G.L.; Snaebjornsson, P.; et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat. Med. 2020, 26, 566–576.

17. Chalabi, M.; Verschoor, Y.L.; van den Berg, J.; Sikorska, K.; Beets, G.; Lent, A.V.; Grootscholten, M.C.; Aalbers, A.; Buller, N.; Marsman, H.; et al. LBA7 Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study. Ann. Oncol. 2022, 33, S1389.
18. Hu, H.; Kang, L.; Zhang, J.; Wu, Z.; Wang, H.; Huang, M.; Lan, P.; Wu, X.; Wang, C.; Cao, W.; et al. Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): A single-centre, parallel-group, non-comparative, randomised, phase 2 trial. Lancet Gastroenterol. Hepatol. 2022, 7, 38–48.
19. Zhou, L.; Yang, X.Q.; Zhao, G.Y.; Wang, F.J.; Liu, X. Meta-analysis of neoadjuvant immunotherapy for non-metastatic colorectal cancer. Front. Immunol. 2023, 14, 1044353.
20. Zhang, X.; Wu, T.; Cai, X.; Dong, J.; Xia, C.; Zhou, Y.; Ding, R.; Yang, R.; Tan, J.; Zhang, L.; et al. Neoadjuvant Immunotherapy for MSI-H/dMMR Locally Advanced Colorectal Cancer: New Strategies and Unveiled Opportunities. Front. Immunol. 2022, 13, 795972.
21. Shiu, K.-K.; Seligmann, J.F.; Graham, J.; Wilson, R.H.; Saunders, M.P.; Iveson, T.; Kayhanian, H.; Khan, K.H.; Rodriguez-Justo, M.; Jansen, M.; et al. NEOPRISM-CRC: Neoadjuvant pembrolizumab stratified to tumor mutation burden for high-risk stage 2 or stage 3 deficient-MMR/MSI-high colorectal cancer. J. Clin. Oncol. 2022, 40, TPS3645.
22. Zhang, J.; Cai, J.; Deng, Y.; Wang, H. Complete response in patients with locally advanced rectal cancer after neoadjuvant treatment with nivolumab. Oncoimmunology 2019, 8, e1663108.
23. Mori, R.; Uemura, M.; Sekido, Y.; Hata, T.; Ogino, T.; Takahashi, H.; Miyoshi, N.; Mizushima, T.; Doki, Y.; Eguchi, H. Locally advanced rectal cancer receiving total neoadjuvant therapy combined with nivolumab: A case report and literature review. World J. Surg. Oncol. 2022, 20, 166.
24. Jin, Z.; Sanhueza, C.T.; Johnson, B.; Nagorney, D.M.; Larson, D.W.; Mara, K.C.; Harmsen, W.C.; Smyrk, T.C.; Grothey, A.; Hubbard, J.M. Outcome of Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Mayo Clinic Experience. Oncologist 2018, 23, 1083–1091.
25. Barraud, S.; Tougeron, D.; Villeneuve, L.; Eveno, C.; Bayle, A.; Parc, Y.; Pocard, M.; André, T.; Cohen, R. Immune checkpoint inhibitors for patients with isolated peritoneal carcinomatosis from dMMR/MSI-H colorectal cancer, a BIG-RENAPE collaboration. Dig. Liver Dis. 2023, 55, 673–678.
26. Tonello, M.; Nappo, F.; Vassallo, L.; Di Gaetano, R.; Davoli, C.; Pizzolato, E.; De Simoni, O.; Tassinari, C.; Scapinello, A.; Pilati, P. Complete pathological response of colorectal peritoneal metastases in Lynch syndrome after immunotherapy case report: Is a paradigm shift in cytoreductive surgery needed? BMC Gastroenterol. 2022, 22, 17.
27. Tominaga, T.; Nonaka, T.; Fukuda, A.; Moriyama, M.; Oyama, S.; Ishii, M.; Sawai, T.; Okano, S.; Nagayasu, T. Pathological complete response to pembrolizumab in patients with metastatic

ascending colon cancer with microsatellite instability. Clin. J. Gastroenterol. 2022, 15, 134–139.

28. Cunningham, D.; Allum, W.H.; Stenning, S.P.; Thompson, J.N.; Van de Velde, C.J.; Nicolson, M.; Scarffe, J.H.; Lofts, F.J.; Falk, S.J.; Iveson, T.J.; et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N. Engl. J. Med. 2006, 355, 11–20.
29. The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group. Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer: A Meta-analysis. JAMA 2010, 303, 1729–1737.
30. Bang, Y.J.; Kim, Y.W.; Yang, H.K.; Chung, H.C.; Park, Y.K.; Lee, K.H.; Lee, K.W.; Kim, Y.H.; Noh, S.I.; Cho, J.Y.; et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): A phase 3 open-label, randomised controlled trial. Lancet 2012, 379, 315–321.
31. Sakuramoto, S.; Sasako, M.; Yamaguchi, T.; Kinoshita, T.; Fujii, M.; Nashimoto, A.; Furukawa, H.; Nakajima, T.; Ohashi, Y.; Imamura, H.; et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N. Engl. J. Med. 2007, 357, 1810–1820.
32. Smyth, E.C.; Verheij, M.; Allum, W.; Cunningham, D.; Cervantes, A.; Arnold, D. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2016, 27, v38–v49.
33. Al-Batran, S.E.; Homann, N.; Pauligk, C.; Goetze, T.O.; Meiler, J.; Kasper, S.; Kopp, H.G.; Mayer, F.; Haag, G.M.; Luley, K.; et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): A randomised, phase 2/3 trial. Lancet 2019, 393, 1948–1957.
34. Pietrantonio, F.; Miceli, R.; Raimondi, A.; Kim, Y.W.; Kang, W.K.; Langley, R.E.; Choi, Y.Y.; Kim, K.M.; Nankivell, M.G.; Morano, F.; et al. Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability as a Biomarker in Gastric Cancer. J. Clin. Oncol. 2019, 37, 3392–3400.
35. Stolze, T.; Franke, S.; Haybaeck, J.; Moehler, M.; Grimminger, P.P.; Lang, H.; Roth, W.; Gockel, I.; Kreuser, N.; Bläker, H.; et al. Mismatch repair deficiency, chemotherapy and survival for resectable gastric cancer: An observational study from the German staR cohort and a meta-analysis. J. Cancer Res. Clin. Oncol. 2023, 149, 1007–1017.
36. An, J.Y.; Kim, K.M.; Kim, Y.M.; Cheong, J.H.; Hyung, W.J.; Noh, S.H. Surgical complications in gastric cancer patients preoperatively treated with chemotherapy: Their risk factors and clinical relevance. Ann. Surg. Oncol. 2012, 19, 2452–2458.
37. Nie, R.C.; Chen, G.M.; Yuan, S.Q.; Kim, J.W.; Zhou, J.; Nie, M.; Feng, C.Y.; Chen, Y.B.; Chen, S.; Zhou, Z.W.; et al. Adjuvant Chemotherapy for Gastric Cancer Patients with Mismatch Repair Deficiency or Microsatellite Instability: Systematic Review and Meta-Analysis. Ann. Surg. Oncol. 2022, 29, 2324–2331.

38. Tran-Minh, M.L.; Lehmann-Che, J.; Lambert, J.; Theou-Anton, N.; Poté, N.; Dior, M.; Mary, F.; Goujon, G.; Gardair, C.; Schischmanoff, O.; et al. Prevalence and prognosis of microsatellite instability in oesogastric adenocarcinoma, NORDICAP 16-01. Clin. Res. Hepatol. Gastroenterol. 2021, 45, 101691.

39. Polom, K.; Marrelli, D.; Roviello, G.; Pascale, V.; Voglino, C.; Rho, H.; Marini, M.; Macchiarelli, R.; Roviello, F. Molecular key to understand the gastric cancer biology in elderly patients-The role of microsatellite instability. J. Surg. Oncol. 2017, 115, 344–350.

40. Janjigian, Y.Y.; Shitara, K.; Moehler, M.; Garrido, M.; Salman, P.; Shen, L.; Wyrwicz, L.; Yamaguchi, K.; Skoczylas, T.; Campos Bragagnoli, A.; et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. Lancet 2021, 398, 27–40.

41. Al-Batran, S.-E.; Lorenzen, S.; Thuss-Patience, P.C.; Homann, N.; Schenk, M.; Lindig, U.; Heuer, V.; Kretzschmar, A.; Goekkurt, E.; Haag, G.M.; et al. Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK. J. Clin. Oncol. 2022, 40, 4003-4003.

42. André, T.; Tougeron, D.; Piessen, G.; de la Fouchardière, C.; Louvet, C.; Adenis, A.; Jary, M.; Tournigand, C.; Aparicio, T.; Desrame, J.; et al. Neoadjuvant Nivolumab Plus Ipilimumab and Adjuvant Nivolumab in Localized Deficient Mismatch Repair/Microsatellite Instability-High Gastric or Esophagogastric Junction Adenocarcinoma: The GERCOR NEONIPIGA Phase II Study. J. Clin. Oncol. 2023, 41, 255–265.

43. Raimondi, A.; Palermo, F.; Prisciandaro, M.; Aglietta, M.; Antonuzzo, L.; Aprile, G.; Berardi, R.; Cardellino, G.G.; De Manzoni, G.; De Vita, F.; et al. TremelImumab and Durvalumab Combination for the Non-OperatIve Management (NOM) of Microsatellite InstabiliTY (MSI)-High Resectable Gastric or Gastroesophageal Junction Cancer: The Multicentre, Single-Arm, Multi-Cohort, Phase II INFINITY Study. Cancers 2021, 13, 2839.

44. Pietrantonio, F.; Raimondi, A.; Lonardi, S.; Murgioni, S.; Cardellino, G.G.; Tamberi, S.; Strippoli, A.; Palermo, F.; Prisciandaro, M.; Randon, G.; et al. INFINITY: A multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). J. Clin. Oncol. 2023, 41, 358-358.

45. Li, S.; Xu, Q.; Dai, X.; Zhang, X.; Huang, M.; Huang, K.; Shi, D.; Wang, J.; Liu, L. Neoadjuvant Therapy with Immune Checkpoint Inhibitors in Gastric Cancer: A Systematic Review and Meta-Analysis. Ann. Surg. Oncol. 2023, 30, 3594–3602.